Synthetic Equivalents of the Taxol C,D Ring System. Examination of Nucleophilic Bicyclic Oxetanes and Less-Strained Acetonide Equivalents

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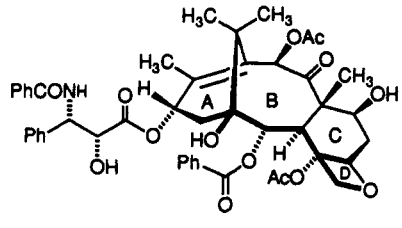
A procedure is described for the conversion of 3-bromo-2-cyclohexenone into the functionalized bicyclic oxetanes **13a** and **13b**. These heterocycles undergo halogen–metal exchange readily in the presence of *tert*-butyllithium at −78 °C, and the resulting vinyl anions are capable of nucleophilic addition to ketones either directly or via cerate intermediates without complication. Whereas norbornenol **20** smoothly undergoes anionic oxy-Cope rearrangement at 0 °C when transformed into its potassium salt, alcohols **23** and **24** are especially prone to aromatization with loss of the oxetane subunit under the same conditions. Thermal activation of these substrates results in fragmentation via an oxy-ene reaction. In order to skirt these complications, attention was directed to O-benzylation of the hydroxy diacetates **9**/**10**, followed by saponification and acetalization with 2,2-dimethoxypropane. This has made available the pair of bromo acetonides **36** and **37**. Sequential treatment of **36** with *tert*-butyllithium and anhydrous cerium trichloride gave the corresponding organocerate that added stereoselectively to the endo surface of the carbonyl group in optically pure ketone **22**. The individual diastereomers thus produced were subjected to anionic oxy-Cope rearrangement in the presence of potassium hexamethyldisilazide and air. In this way, the highly reactive enolates formed by [3,3] sigmatropy were directly oxygenated. The resulting α-hydroxy ketones were examined for their ability to experience dehydration. While **42** underwent spontaneous regiospecific conversion to α,β-unsaturated ketone **43** during formation of its mesylate, **41** proved resistant to the loss of water. This striking difference in reactivity has been analyzed on the basis of the conformational features of the two diastereomers as deduced by molecular mechanics calculations and X-ray crystallography.

Taxol (**1**) has been heralded as a promising anticancer drug on the strength of its efficacy in the treatment of ovarian, breast, and lung tumors.[2] Its potential as a new drug of major consequence has commanded the unrivaled attention of many diverse segments of the scientific community.[3] The unusual mode of action of **1**, which has the remarkable capacity for stabilizing microtubule assembly,[4] is intrinsically exciting because of its unprecedented nature. The limited availability of taxol for patient use has caused many research groups to seek and develop a practical scheme for synthesizing **1** and analogues of this fascinating molecule.[5,6]



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Our convergent approach to taxol is founded on the premise that inexpensive and readily available (1*R*)-(+)-camphor (**2**) can serve as a key component in its construction, since **2** possesses the proper absolute configuration for the entire left-half portion of **1**. Already detailed has been our ability to condense a derivative of **2** with a cyclohexenyl bromide exemplified by **3**,[7] to achieve sub-

(1) National Institutes of Health Postdoctoral Fellow, 1991-1992.

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(4) (a) Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature* **1979**, *277*, 665. (b) Parness, J.; Horwitz, S. B. *J. Cell. Biol.* **1981**, *91*, 479. (c) Manfredi, J. J.; Horwitz, S. B. *Pharmac. Ther.* **1984**, *25*, 83.

(5) Reviews: (a) Lythgoe, B. *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1968; Vol. 10, p 597 ff. (b) Suffness, M.; Cordell, G. A. *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 25, p 1 ff. (c) Blechert, S.; Guenard, D. *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1990; Vol. 39, p 195 ff. (d) Swindell, C. S. *Org. Prep. Proced. Int.* **1991**, *23*, 465. (e) Paquette, L. A. *Studies in Natural Products Chemistry*; Rahman, A. U., Ed.; Elsevier: Amsterdam, 1992; Vol. 11, p 3 ff.

(6) More recent work: (a) Yadav, J. S.; Ravishankar, R. *Tetrahedron Lett.* **1991**, *32*, 2629. (b) Sakan, K.; Smith, D. A.; Babirad, S. A.; Fronczek, F. R.; Houk, K. N. *J. Org. Chem.* **1991**, *56*, 2311. (c) Wender, P. A.; Mucciaro, T. P. *J. Am. Chem. Soc.* **1992**, *114*, 5878. (d) Saha, G.; Karpha, R.; Roy, S. S.; Ghosh, S. *J. Chem. Soc. Perkin Trans. 1* **1992**, 1587. (e) Jackson, R. W.; Higby, R. G.; Gilman, J. W.; Shea, K. J. *Tetrahedron* **1992**, *48*, 7013. (f) Magee, T. V.; Bornmann, W. G.; Isaacs, R. C. A.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 3274. (g) Queneau, Y.; Krol, W. J.; Bornmann, W. G.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 4043. (h) Blechert, S.; Kleine-Klausing, A. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 412. (i) Blechert, S.; Müller, R.; Beitzel, M. *Tetrahedron* **1992**, *48*, 6953. (j) Nicolaou, K. C.; Hwang, C.-K.; Sorensen, E. J.; Clairborne, C. F. *J. Chem. Soc., Chem. Commun.* **1992**, 1117. (k) Nicolaou, K. C.; Liu, J. J.; Hwang, C.-K.; Dai, W.-M.; Guy, R. K. *J. Chem. Soc., Chem. COmmun.* **1992**, 1118. (l) Benchikh le-Hocine, M.; Do Khac, D.; Fetizon, M.; Guir, F.; Guo, Y.; Prangé, T. *Tetrahedron Lett.* **1992**, *33*, 1443. (m) Benchikh le-Hocine, M.; Do Khac, D.; Fetizon, M. *Synth. Commun.* **1992**, *22*, 245. (n) Winkler, J. D.; Subrahman-yam, D. *Tetrahedron* **1992**, *48*, 7049. (o) Kataoka, Y.; Nakamura, Y.; Morihara, K.; Arai, H.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1992**, *33*, 6979. (p) Morihara, K.; Seto, M.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1993**, *34*, 345. (q) Golinski, M.; Vasudevan, S.; Floresca, R.; Brock, C. P.; Watt, D. S. *Tetrahedron Lett.* **1993**, *34*, 55. (r) Oh, J.; Choi, J.-R.; Cha, J. K. *J. Org. Chem.* **1992**, *57*, 6664. (s) Kraus, G. A.; Zheng, D. *Synlett* **1993**, 71. See also ref 31.

(7) (a) Paquette, L. A.; Pegg, N. A.; Toops, D.; Maynard, G. D.; Rogers, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 277. (b) Paquette, L. A.; Combrink, K. D.; Elmore, S. W.; Rogers, R. D. *J. Am. Chem. Soc.* **1991**, *113*, 1335. (c) Pegg, N. A.; Paquette, L. A. *J. Org. Chem.* **1991**, *56*, 2461. (d) Elmore, S. W.; Combrink, K. D.; Paquette, L. A. *Tetrahedron Lett.* **1991**, *32*, 6679.

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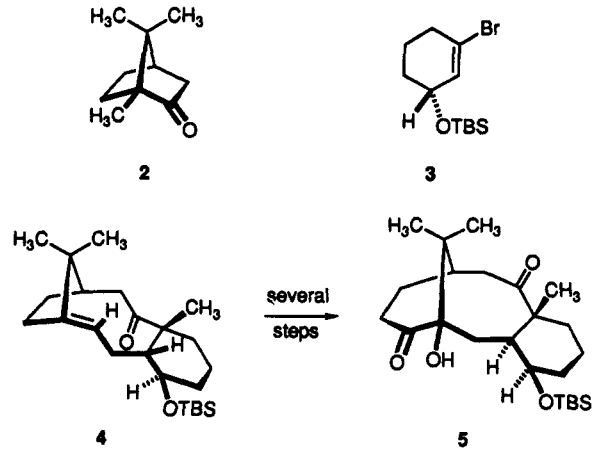
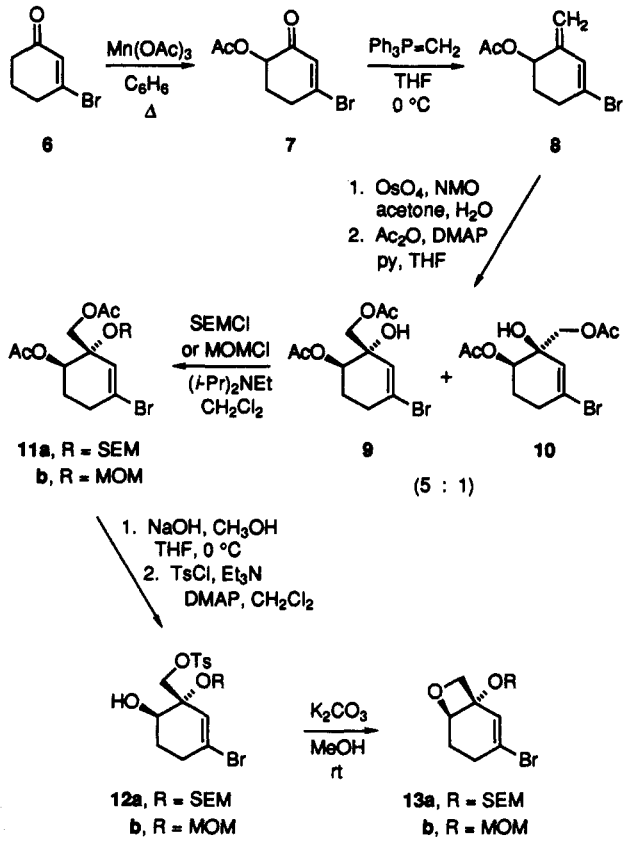


sequent anionic oxy-Cope rearrangement of these 1,2-adducts to give ketones such as **4**, and to implement bridge migration within structurally modified **4** so as to produce **5**.[8]

Scheme I



Further simplification of this pathway would be realized if the chemotherapeutically vital[9] oxetane D ring could be incorporated into a vinyl bromide such as **3** and carried through to an intermediate equivalent to **5**, with ultimate arrival at the target. The present paper describes the preparation of a pair of bromine-containing bicyclic oxetanes, details model studies demonstrating their suitable nucleophilicity, and explores the stability of the oxetane subunit to the strongly basic conditions associated with the [3,3] sigmatropic step.

Indeed, a vinyl anion containing the 3-oxetanol substructure present in taxol can be conveniently produced, readily captured by β,γ-unsaturated ketones, and carried intact through certain kinetically accelerated anionic oxy-Cope rearrangements. However, when the rate of the [3,3] sigmatropic rearrangement is slowed to some degree, the strongly alkaline conditions of the last reaction were found to promote competitive destruction of the oxetane ring. Since the degradative process was singularly adopted in those systems that were destined to serve as potential precursors of taxol, consideration was subsequently given to releasing strain within the heterocyclic ring in a fashion that would allow for ready assembly of the oxetane at a later stage of the synthesis.

The experiments that constitute a resolution of this complication are also described. In addition, by performing the key isomerization in the presence of oxygen, it has proven possible to directly incorporate a hydroxyl group efficiently at C8. The striking difference in the dehydratability of these stereoisomeric α-hydroxy ketones is presented and interpreted on the basis of their individual conformational features as deduced by molecular mechanics calculations and X-ray methods. Finally, the unreactivity of the resultant α,β-unsaturated ketone toward Michael additions is discussed.

Results and Discussion

Preparation of the Vinyl Bromides. With but one exception,[10] the several ingenious methods heretofore developed for gaining access to 3-oxetanols structurally related to the taxol D ring have invariably relied on the intermediacy of a suitably activated triol precursor.[6f,11,12] Since this strategy has also seen successful application in the context of taxane hemisynthesis,[13] it was adopted here. To this end, 3-bromo-2-cyclohexenone (**6**)[14] was heated with $Mn(OAc)_3$ in benzene[15] to effect α-acetoxylation[16,17] (Scheme I). Oxidized product **7** responded well to Wittig olefination, affording **8** in 69% yield. This allylic acetate was attacked in a totally regioselective manner at its exocyclic double bond when treated with a catalytic quantity of OsO_4 in the presence of NMO.[18] Since acetyl transfer was found to operate to a limited extent under these reaction conditions, acetylation was performed prior to analysis of the product distribution. The ratio of **9** to **10** was 5:1. Although the relative configuration of the major diastereomer could not be unequivocally assigned

(8) (a) Paquette, L. A.; Elmore, S. W.; Combrink, K. D.; Hickey, E. R.; Rogers, R. D. *Helv. Chim. Acta* **1992**, *75*, 1755. (b) Paquette, L. A.; Combrink, K. D.; Elmore, S. W.; Zhao, M. *Helv. Chim. Acta* **1992**, *75*, 1772.

(9) Samaranayake, G.; Magri, N. F.; Jitrangsri, C.; Kingston, D. G. I. *J. Org. Chem.* **1991**, *56*, 5114.

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(11) Berkowitz, W. F.; Amarasekara, A. S. *Tetrahedron Lett.* **1985**, *26*, 3663.

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(13) Ettouati, L.; Ahond, A.; Poupat, C.; Potier, P. *Tetrahedron* **1991**, *47*, 9823.

(14) Denmark, S. E.; Habermas, K. L.; Hite, G. A.; Jones, T. K. *Tetrahedron* **1986**, *42*, 2821.

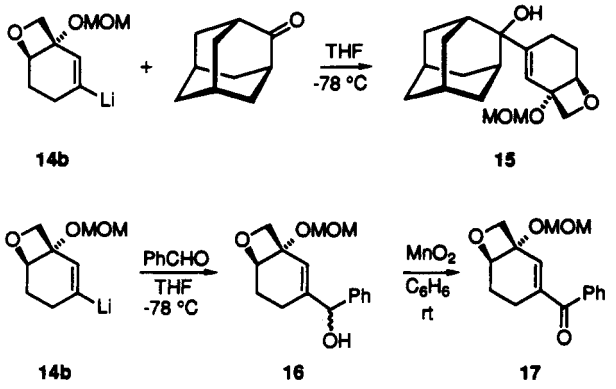
(15) (a) Williams, G. J.; Hunter, N. R. *Can. J. Chem.* **1976**, *54*, 3830. (b) Dunlap, N. K.; Sabol, M. R.; Watt, D. S. *Tetrahedron Lett.* **1984**, *25*, 5839. (c) Demir, A. S.; Jeganathan, A.; Watt, D. S. *J. Org. Chem.* **1989**, *54*, 4020. (d) Demir, A. S.; Sayrac, T.; Watt, D. S. *Synthesis* **1990**, 1119.

(16) Subsequent to the completion of this phase of our work, an independent preparation of **7** was reported: Banwell, M. G.; Lambert, J. N.; Richards, S. L. *Aust. J. Chem.* **1991**, *44*, 939.

(17) Treatment of **6** with $Mn(OAc)_3$ in the presence of benzoic, chloroacetic, isobutyric, or pivalic acid afforded the corresponding α-benzoate, chloroacetate, isobutyrate, or pivalate ester in yields of 16, 48, 24, and 13%, respectively.

(18) (a) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973. (b) Schröder, M. *Chem. Rev.* **1980**, *80*, 187.

Scheme II



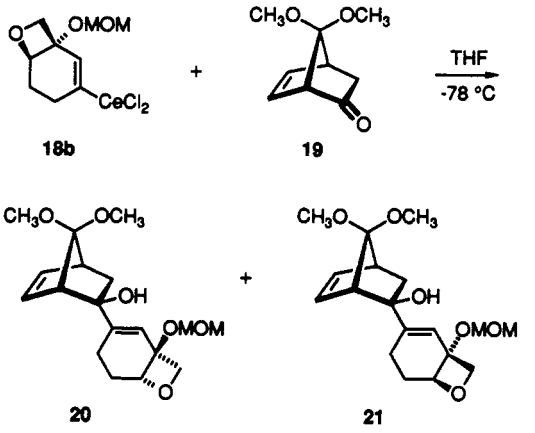
on spectroscopic grounds, preferential attack on the π-face anti to that flanked by the acetoxyl group could be reliably assumed on the basis of precedent.[19,20]

Once the tertiary hydroxyl group had been protected as either the silylethoxymethyl (SEM)[21] or MOM ether,[22] conversion to monotosylates **12a** and **12b** was performed in order to set the stage for ensuing ring closure and formation of both **13a** and **13b**. Oxetane formation was most efficiently accomplished (73–81%) when performed in the presence of K_2CO_3 and methanol at room temperature.

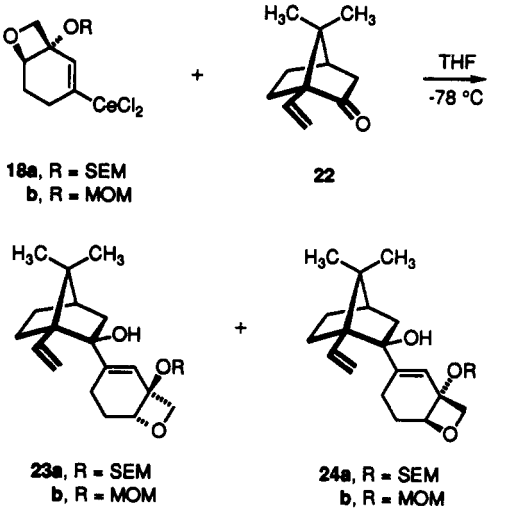
Condensation Reactions of 13. Full implementation of the plan to utilize bromides **13a** and **13b** as nucleophilic reagents required that halogen–metal exchange be effected under conditions that would not cleave the relatively sensitive oxetane ring. Our purposes were best served by exposure of these bromides to 2 equiv of *tert*-butyllithium in THF at −78 °C. Once generated in this manner, vinyllithiums **14a** and **14b** were noted to be reasonably stable entities if maintained at this temperature. In early probe experiments, **14b** was treated with both 2-adamantanone and benzaldehyde (Scheme II). In the first instance, the ketone does not possess a prochiral carbonyl group. Consequently, **15** was isolated as an isomerically pure, racemic crystalline substance in 73% yield. Where benzaldehyde is concerned, a mixture of diastereomeric alcohols **16** resulted (77%). These were not separated, but directly oxidized to **17** with manganese dioxide.

The next stage of the investigation consisted of the addition of these anions to 7,7-disubstituted bicyclic ketones **19**[23] and **22**.[24] Since the presence of a syn C-7 substituent sterically disallows exo approach of the nucleophile and simple enolization must be abated during endo attack,[7a,25] recourse was made to organocerate reagents. When the standard conditions[26] for such processes were applied, **18b** added smoothly to **19** to give the two diastereomeric alcohols **20** and **21** in a 10:1 ratio

Scheme III



Scheme IV



(Scheme III). The major stereoisomer was deduced to be **20** on the strength of subsequent isomerization chemistry to be described below.

The vinylcerates formally depicted as **18a** and **18b** added smoothly to **22** (73–80%). In the SEM series, the pair of diastereomeric alcohols formed in a 1.5:1 ratio (Scheme IV). Although **23a** and **24a** differ significantly in polarity and therefore proved to be chromatographically separable, neither was crystalline and a clearcut structural distinction between them was not possible. The MOM derivatives **23b** and **24b** (produced as a 1:1 mixture) were not separable by flash chromatography.

Oxyanionic Sigmatropy. Exo alcohols derived from bicyclic ketone **19** are recognized to possess latent oxy-Cope reactivity well above the norm.[27] Thus, the α-naphthyl and benzofuranyl derivatives **25**[28] and **26**[29] undergo facile [3,3] sigmatropic rearrangement when heated with sodium hydride in THF. Comparable feats are not easily accomplished in other systems[30] because of the need to disrupt aromatic character temporarily. We reasoned by extrapolation that the potassium alkoxide of **20** should

(19) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943. (b) Christ, W. J.; Cha, J. K.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3947.

(20) The pivalate analogue of 8 underwent osmylation with a stereoselectivity of only 3:1 (91% combined yield). Obviously, an increase in the steric bulk of the acyl protecting group need not translate into an increased kinetic preference for anti attack. No evidence for transfer of the pivalate group was uncovered.

(21) Lipshutz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, *21*, 3343.

(22) Kluge, A. F.; Untch, K. G.; Fried, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 7827.

(23) Jung, M. E.; Hudspeth, J. P. *J. Am. Chem. Soc.* **1977**, *99*, 5508.

(24) Fischer, N.; Opitz, G. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 877.

(25) Paquette, L. A.; Learn, K. S.; Romine, J. L.; Lin, H.-S. *J. Am. Chem. Soc.* **1988**, *110*, 879.

(26) (a) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233. (b) Imamoto, T.; Sugiura, Y. *J. Organometal. Chem.* **1985**, *285*, C21. (c) Imamoto, T.; Takiyama, N.; Nakamura, K. *Tetrahedron Lett.* **1985**, *26*, 4763. (d) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.

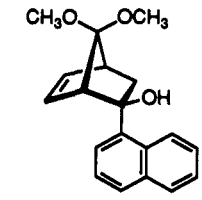
(27) Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609.

(28) Jung, M. E.; Hudspeth, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 4309.

(29) Jung, M. E.; Hudspeth, J. P. *J. Am. Chem. Soc.* **1980**, *102*, 2463.

(30) Paquette, L. A.; Maleczka, R. E., Jr. *J. Org. Chem.* **1993**, *58*, in press.

exhibit a notably heightened rate of isomerization to **27**. Indeed, treatment of **20** with an excess of potassium hexamethyldisilazide and 18-crown-6 in THF at 0 °C led to complete disappearance of the alcohol within minutes. These conditions provided for the isolation of **27** in 80% yield. Clearly, the oxetane ring suffers no deleterious effect under these circumstances.



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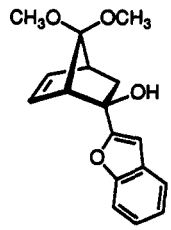

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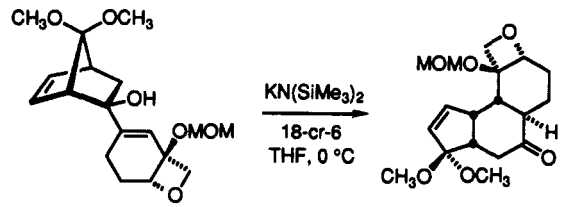
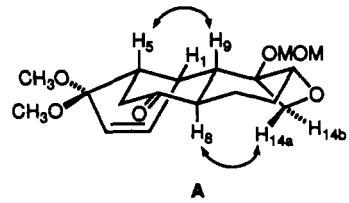


20 **27**

Since the relative stereochemical features of **20** had not yet been deduced conclusively, **27** could be one of four possible diastereomers. A doubling of the options arises because of the potential for protonating the intermediate enolate so as to deliver either a cis or trans B/C-fused product. Recourse to COSY and NOESY experiments established decisively that the absolute configuration of **27** is as shown. For example, COSY confirmed that the B/C ring juncture is indeed trans on the strength of the coupling constants determined for H1,H9 (6.5 Hz), and H8,H9 (14.1 Hz) (see **A**). Further, the W-coupling



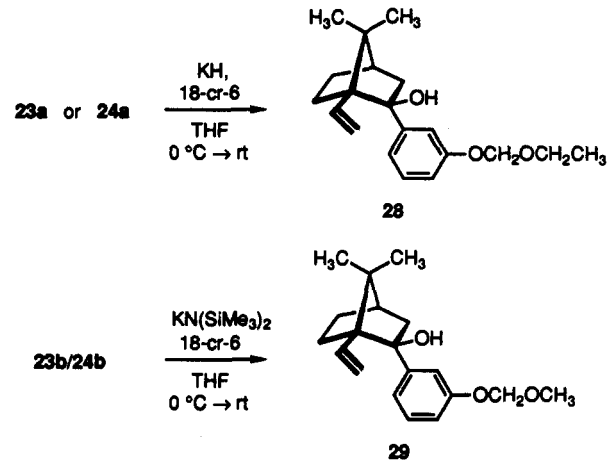
A

observed between H9 and the more downfield H14b signal is uniquely accommodated by **27**.

The NOESY plots were characterized by strong cross-peaks between H5 and H9, as well as between the H8 and high-field H14a combination. Accordingly, these pairs of protons must reside in close proximity as shown in **A** and found only in **27**.

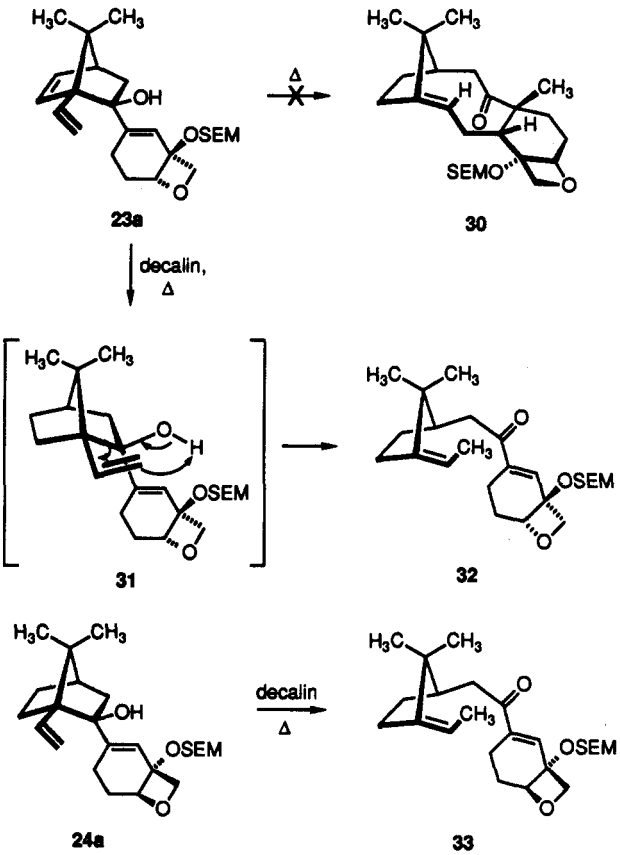
In contrast, 1-vinyl-7,7-dimethyl-*exo*-2-norbornanols such as **23** and **24** have been reported to undergo anionic oxy-Cope rearrangement in the vicinity of room temperature.[7a] Chirality transfer is complete and predictable because an endo-chair transition state is invariably adopted.[7,8] In order to assess the possible consequences of these rate differences, **23a** (or **24a**) was treated in the conventional way with various potassium bases in the presence of 18-crown-6 (Scheme V). Under these conditions, the desilylated and aromatized product **28** was formed in modest yield. The **23b/24b** diastereomer mixture underwent similar conversion to **29**. In both series, the kinetically preferred reaction would appear to be an elimination

Scheme V



28 **29**

Scheme VI



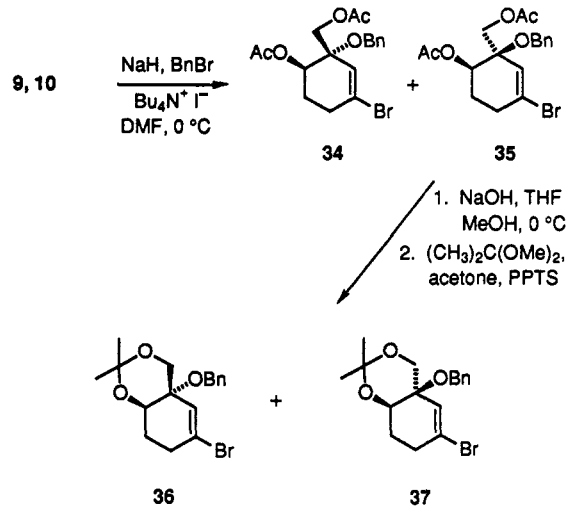
23a **30** **31** **32** **24a** **33**

that cleaves the oxetane ring and generates a 1,4-cyclohexadiene moiety, which subsequently suffers oxidation with the loss of formaldehyde. In the SEM series, desilylation of the hydroxyl-protecting group also takes place, but without the E_2 component that usually liberates the functional group.

Avoidance of the strongly basic conditions was also not conducive to delivering desired ketonic products such as **30** (Scheme VI). Rather, the independent heating of **23a** and **24a** in solvents such as decalin and *N*-methylpyrrolidinone resulted in smooth operation of an oxy-ene reaction (see **31**)[31] to afford **32** and **33**, respectively. Therefore, although the oxetane ring survives such thermal

(31) For other examples of ene behavior in oxy-Cope precursors, see: (a) Snider, B. B.; Allentoff, A. J. *J. Org. Chem.* **1991**, *56*, 321. (b) Zucker, P. A.; Lupia, J. A. *Synlett* **1990**, 729.

Scheme VII



activation, the frangibility of the vinylbornanols does not allow for operation of the sigmatropic reorganization that would involve both of their double bonds.

Thus, although bicyclic oxetanes such as **13** can be prepared and utilized as nucleophiles in various contexts, the presence of these building blocks in substrates exemplified by **23** and **24** is not conducive to adoption of the oxyanionic Cope rearrangement pathway. Since **20** does undergo [3,3] sigmatropic isomerization, the complication may stem from nonbonded steric interactions present in those transition states required for oxy-Cope rearrangement within **23** and **24**, but appreciably minimized as **20** adopts the requisite activated geometry.

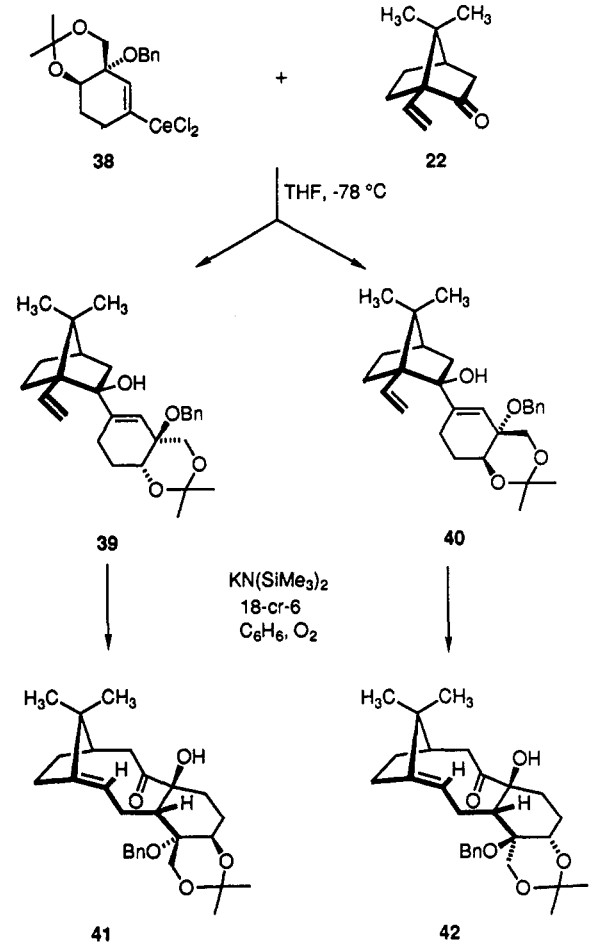
Attempts to accelerate the rate of [3,3] sigmatropy[32] within **23** and **24** by replacing the vinyl group by *E*- and *Z*-vinyl ether substituents met with a similar fate,[33] once again a likely consequence of excessive steric congestion.

The ultimate resolution of this dilemma would appear to involve the incorporation of a less-sensitive and less-bulky pro-oxetane heterocyclic subunit that would allow for oxy-Cope rearrangement, while being subsequently amenable to modest structural modification. The workability of this alternative plan is presented below.

Less-Strained Acetonide Equivalents. O-Benzylation of the **9/10** mixture of diastereomers by treatment with sodium hydride and benzyl bromide in the presence of 10 mol% tetra-*n*-butylammonium iodide[34] afforded **34** and **35** in 83% combined yield (Scheme VII). Although the two products could be separated at this stage, convenience was served by effecting the subsequent saponification and conversion to **36** and **37** without prior chromatographic purification. In this way, reasonable quantities of pure **36** (66%) and pure **37** (12%) could be acquired with minimal effort. Both acetonides were colorless solids. Their structural features could be confidently deduced to be as shown on the strength of chemical interconversions earlier performed on **9**.

The coupling of **36** to optically pure ketone **22**[24] was accomplished via the organocerium derivative, displayed as the dichloride **38** exclusively on the basis of stoichiometry. Most often, the diastereoselectivity associated with endo addition of a chiral, racemic vinyl anion to a 2-norbornanone is steeply biased toward a matched

Scheme VIII



combination.[25,35] In the present circumstances, the more polar diastereomer **40** was favored over **39** by a ratio of 1.2:1 because only a modest excess of the vinyl cerate was employed (Scheme VIII).

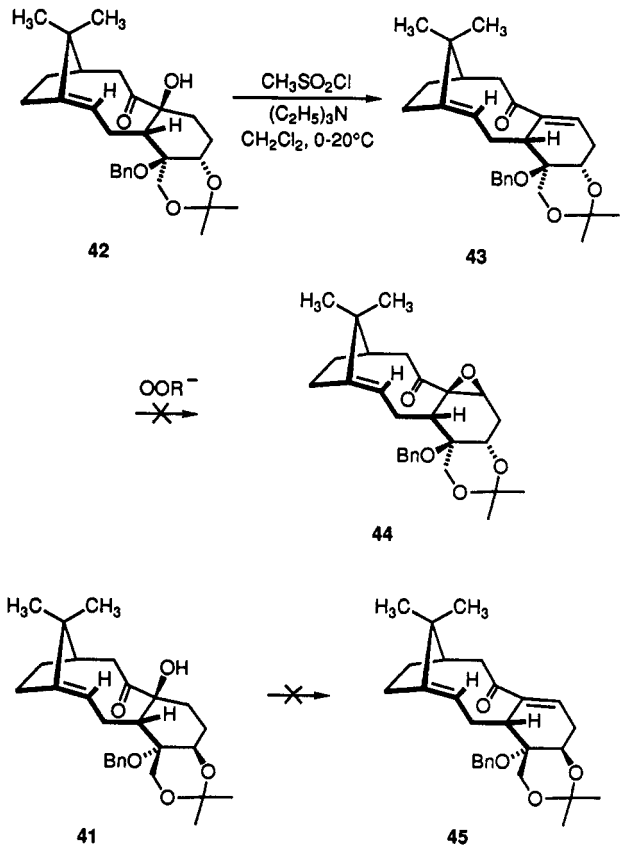
At this juncture, the relative configuration of the 1,3-dioxane ring in the two carbinols, which could be separated chromatographically, could not be assigned with certainty. Consequently, these compounds were individually subjected to standard anionic oxy-Cope conditions and found to undergo the intended sigmatropic rearrangement. These reactions were intentionally performed in the presence of air in order that the intermediate enolates would experience spontaneous α-oxygenation[36] to give **41** and **42**. α-Ketol **42** proved to be a highly crystalline substance, and its stereochemical constitution was therefore established by means of X-ray crystallography. Note that **42** (79%) is formed more efficiently than **41** (53%), despite the need to involve a comparably congested oxy-Cope transition state.[7a] It is, of course, possible that the complication stems from different electronic contributions exerted by the allylic C–O bond properly oriented stereoelectronically in **40** but not in **39**.

The dehydration of **42**, readily achieved by spontaneous elimination of the derived mesylate, afforded **43** as the only characterizable product (Scheme IX). The high regioselectivity of this process is noteworthy. In contrast,

(32) Curran, D. P.; Suh, Y.-G. *J. Am. Chem. Soc.* **1984**, *106*, 5002.
(33) Thompson, R. C., unpublished results.
(34) Thompson, R. C.; Paquette, L. A., unpublished.

(35) (a) Paquette, L. A.; Learn, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 7873. (b) Paquette, L. A.; Romine, J. L.; Lin, H.-S.; Wright, J. *J. Am. Chem. Soc.* **1990**, *112*, 9284.
(36) Paquette, L. A.; DeRussy, D. T.; Pegg, N. A.; Taylor, R. T.; Zydowsky, T. M. *J. Org. Chem.* **1989**, *54*, 4576.

Scheme IX



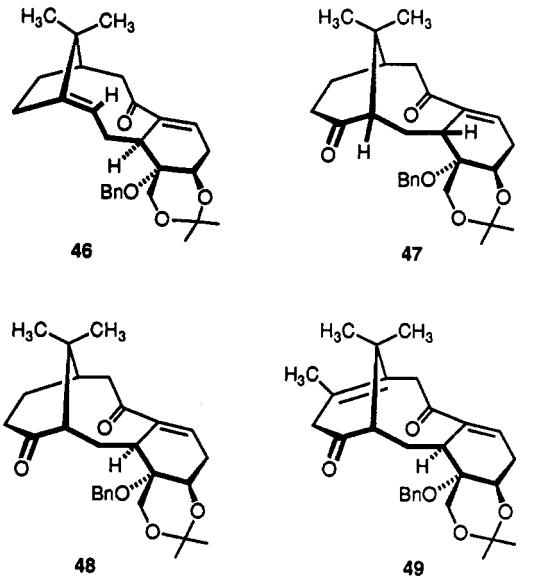
42 43 44 41 45

α-ketol **41**, the diastereomer specifically suited to our quest of taxol, could not be induced to experience the loss of water and deliver **45** or an isomer thereof. These transformations were of interest because of our desire to develop a means for introducing the 7-hydroxy-8-methyl substitution characteristic of the taxol C-ring.[37]

The proclivity of **42** for facile dehydration can be appreciated on the basis of its rather rigid conformational features as gauged from the perspective drawing adapted from the crystallographic data (Figure 1A). Thus, in the particular arrangement adopted by this molecule, the tertiary hydroxyl finds itself oriented gauche to the adjoining methine hydrogen, but aligned in a perfectly antiperiplanar manner to the α-proton of the flanking methylene group (see arrows). The global minimum energy conformation of **41**, as generated on the basis of molecular mechanics calculations,[38] is likely rigidly fixed. However, as seen in Figure 1B, its hydroxyl is not only gauche to the vicinal tertiary C–H bond, but also oriented in a manner that causes it to bisect the H–C–H angle adopted by the adjacent methylene carbon. Evidently, **41** does not experience a change in geometry sufficient to allow operation of either a syn or anti elimination, even under forcing conditions.

The unusual inflexibility of these systems surfaces in other contexts as well. For example, **43** has been found not to undergo epoxidation under alkaline peroxide conditions of various types.[40] Structural models reveal the carbonyl π-bond in **43** to be held forcibly in a downward-oriented direction (as illustrated in the formula) such that conjugation with the adjacent double bond is not possible. This strong conformational bias rules out the possible operation of a Michael addition reaction since only a nonplanar enolate anion could result and resonance delocalization would not be available.

Consideration of related structures such as **46–48** indicates that this complication may be far more pervasive than originally perceived.[5] All three of these examples give convincing indication of lacking conformational mobility, such that the prospects of achieving coplanarity about the enone chromophore appears equally improbable. This state of affairs is not at all relieved when a bridgehead double bond is inserted as in **49**.



46 47 48 49

In our view, the inability of the B-ring carbonyl subunit in this collective group of possible taxol precursors to orient itself in-plane with the adjacent double bond foreshadows an inability to introduce the C-7 hydroxyl of taxol in this manner. A more viable tactic would appear to involve the introduction of this key functional group at a much earlier stage of synthetic development by a means that would also incorporate the C8 methyl group in order to deter the possible elimination of water. These objectives are currently being pursued in this laboratory.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1320 spectrometer. ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at both 75 and 62.5 MHz (as indicated) on Bruker instruments at The Ohio State University Campus Chemical Instrument Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. The chromatographic separations were carried out under flash conditions on Woelm 230–400 mesh silica gel. The organic extracts were dried over anhydrous sodium sulfate. Solvents were reagent grade and in many cases dried prior to use.

(±)-3-Bromo-6-hydroxy-2-cyclohexen-1-one Acetate (7). A benzene solution (300 mL) of $Mn(OAc)_3$ (40.0 g) was refluxed under a Dean–Stark trap and nitrogen atmosphere for 2.5 h to remove water. Following a return to rt, a solution of **6** (7.0 g,

(37) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.

(38) Each of the structures was minimized using MODEL version KS 2.96.[39] Through use of the Grid Search function within MODEL, a multiconformer run was performed within each molecule incorporating the four rings of the tetracycle. In each instance, over 150 conformers were generated and minimized to ensure arrival at the global minimum energy coformer. The MMX software package was then used to optimize the lowest energy conformer in each case.

(39) Still, W. C.; Steliou, K., private communication.

(40) Daniels, K.; Thompson, R. C., unpublished results.

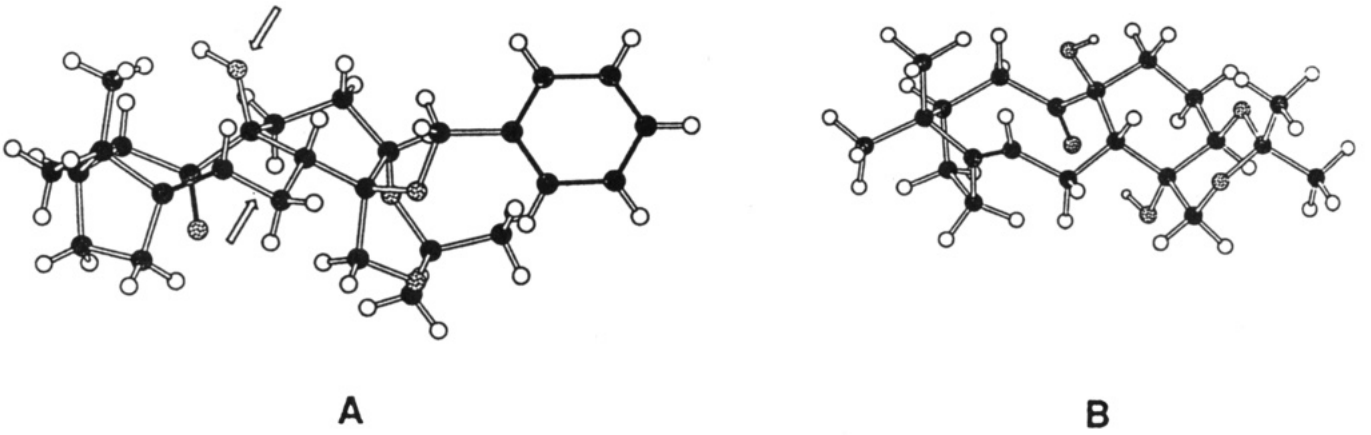


Figure 1. Crystallographically adapted ground state structure **A** of α-hydroxy ketone **42**, and **B**, global minimum energy conformation of α-hydroxy ketone **41**, with the benzyl group omitted for clarity (Chem 3-D output).

0.040 mol) in benzene (15 mL) was introduced, the mixture was refluxed for 18 h, and concentration to a volume of ca. 200 mL was achieved. Water (200 mL) was added, the mixture was cooled to rt, and the product was extracted into ether (2 × 200 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution (200 mL) and brine (200 mL) prior to drying and concentration in vacuo. Purification of the residue by flash chromatography on silica gel (elution with 2:1 hexane–ethyl acetate) gave **7** as a reddish oil (6.45 g, 69%) which solidified. Bulb-to-bulb distillation (140 °C, 0.1 Torr) provided a white solid: mp 42–44 °C; IR (neat, cm^{-1}) 1750, 1700, 1605; ^1H NMR (300 MHz, $CDCl_3$) δ 6.46 (d, J = 2.4 Hz, 1 H), 5.34–5.27 (m, 1 H), 3.10–2.87 (m, 2 H), 2.26–2.16 (m, 2 H), 2.14 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 190.6, 170.0, 148.9, 131.1, 72.1, 35.6, 28.5, 20.7; MS m/z (M^+) calcd 231.9735, obsd 231.9738. Anal. Calcd for $C_8H_9BrO_3$: C, 41.23; H, 3.89. Found: C, 41.12; H, 3.93.

(±)-4-Bromo-2-methylene-3-cyclohexen-1-ol Acetate (8). A THF solution (150 mL) of methyltriphenylphosphonium bromide (12.6 g, 35.3 mmol) was cooled to 0 °C under N_2 and treated with n-butyllithium (29.5 mL of 1.2 M in hexane, 35.4 mmol), stirred at 0 °C for 12 min, and admixed with a solution of **7** (6.75 g, 29.0 mmol) in THF (20 mL). After 15 min, saturated NH_4Cl solution (10 mL) and water (10 mL) were introduced, and the mixture was warmed to rt, diluted with more water (150 mL), and extracted with ether (2 × 150 mL). The combined organic phases were dried and concentrated, and the residue was purified by flash chromatography (silica gel, elution with 10:1 hexane–ethyl acetate) to give **8** as a pale yellow oil (4.62 g, 69%); IR (neat, cm^{-1}) 1735, 1630, 1240; ^1H NMR (300 MHz, $CDCl_3$) δ 6.49 (s, 1 H), 5.48 (m, 1 H), 5.09 (s, 1 H), 5.00 (s, 1 H), 2.76–2.54 (m, 2 H), 2.07 (s, 3 H), 2.01–1.93 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.3, 140.4, 129.8, 125.3, 114.8, 69.3, 32.2, 29.0, 21.2; MS m/z (M^+ – HOAc) calcd 169.9731, obsd 169.9665. This product is very labile and should be used immediately.

(±)-*trans*-4-Bromo-2-(hydroxymethyl)-3-cyclohexene-1,2-diol α,1-Diacetate and (±)-*cis*-4-Bromo-2-(hydroxymethyl)-3-cyclohexene-1,2-diol α,1-Diacetate (9 and 10). To a solution of N-methylmorpholine N-oxide monohydrate (4.44 g, 32.8 mmol) in water (15 mL) and *tert*-butyl alcohol (1.2 mL) was added **8** (3.324 g, 14.4 mmol) dissolved in acetone (15 mL). Osmium tetroxide (9.5 mg, 0.037 mmol) was introduced, stirring was continued for 24 h at rt, and a slurry consisting of Florisil (2 g), sodium thiosulfate (1.5 g), and water (5 mL) was added. After being stirred overnight, the mixture was filtered through Celite, diluted with brine (30 mL), and extracted with ethyl acetate (3 × 25 mL). The combined organic phases were dried and concentrated, and the residue was subjected to flash chromatography (silica gel, elution with 1:1 hexane–ethyl acetate followed by ethyl acetate alone) to give a faintly yellow oil (3.309 g, 87%).

A 1.842 g (6.95 mmol) sample of this mixture was dissolved in THF (10 mL), cooled to 0 °C, and treated sequentially with acetic anhydride (0.80 mL, 8.5 mmol), pyridine (0.70 mL, 8.7 mmol), and 4-(dimethylamino)pyridine (18 mg, 0.15 mmol). After 10 min at 0 °C, the reaction mixture was warmed to room temperature, stirred for 30 min, quenched with 5% HCl (20 mL), and extracted with ether (2 × 25 mL). The combined organic phases were dried and concentrated and the residue was purified by flash chromatography on silica gel (gradient elution with 5:1 to 2:1 hexane–ethyl acetate) to give 1.775 g (83%) of a 5:1 mixture of **9** and **10**. The diastereomers were separated by MPLC (silica gel, elution with 1:1 hexane–ethyl acetate).

For **9**: colorless oil; IR (neat, cm^{-1}) 3480, 1745, 1650; ^1H NMR (300 MHz, $CDCl_3$) δ 5.94 (s, 1 H), 5.00 (dd, J = 6.3, 2.6 Hz, 1 H), 4.13 (ABq, J = 11.5 Hz, $\Delta\nu$ = 75.7 Hz, 2 H), 2.89 (br s, 1 H), 2.61–2.49 (m, 2 H), 2.18–1.95 (m, 2 H), 2.07 (s, 3 H), 2.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 171.0, 170.3, 128.3, 127.4, 72.3, 71.0, 66.9, 31.8, 24.6, 20.9, 20.7; FAB MS m/z (M^+ + 1) calcd 307.02, obsd 307.03. Anal. Calcd for $C_{11}H_{15}BrO_5$: C, 43.02; H, 4.92. Found: C, 43.05; H, 5.05.

For **10**: colorless oil; IR (neat, cm^{-1}) 3480, 1750, 1655; ^1H NMR (300 MHz, $CDCl_3$) δ 5.98 (t, J = 1.7 Hz, 1 H), 4.97 (dd, J = 9.6, 3.3 Hz, 1 H), 4.04 (ABq, J = 11.5 Hz, $\Delta\nu$ = 47.0 Hz, 2 H), 2.61–2.56 (m, 2 H), 2.53 (br s, 1 H), 2.19–2.07 (m, 1 H), 2.10 (s, 3 H), 2.09 (s, 3 H), 1.96–1.86 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.7, 170.2, 128.6, 128.1, 72.0, 70.2, 67.0, 33.2, 24.8, 21.1, 20.7; FAB MS m/z (M^+ + 1) calcd 307.02, obsd 307.04.

(±)-*trans*-3-Bromo-6-hydroxy-1-[[2-(trimethylsilyl)ethoxy]-methoxy]-2-cyclohexene-1-methanol Diacetate (11a). A solution of the preceding diacetate mixture (1.535 g, 5.00 mmol) in CH_2Cl_2 (10 mL) was treated with SEMCl (1.81 mL, 10.2 mmol) and diisopropylethylamine (2.6 mL, 14.9 mmol). After being stirred for 48 h at rt, the reaction mixture was quenched by the addition of 5% HCl (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried and concentrated, and the residue was purified by flash chromatography (silica gel, elution with 5:1 hexane–ethyl acetate) to give a colorless oil (2.062 g, 94%). Separation of the diastereomers was possible by MPLC (silica gel, elution with 3:1 hexane–ethyl acetate).

For **11a**: IR (neat, cm^{-1}) 1740, 1640, 1370, 1250, 1050; ^1H NMR (300 MHz, $CDCl_3$) δ 6.00 (s, 1 H), 5.14 (dd, J = 6.1, 2.5 Hz, 1 H), 4.79 (ABq, J = 7.7 Hz, $\Delta\nu$ = 26.8 Hz, 2 H), 4.23 (ABq, J = 11.8 Hz, $\Delta\nu$ = 40.3 Hz, 2 H), 3.70–3.50 (m, 2 H), 2.55–2.50 (m, 2 H), 2.15–1.88 (m, 2 H), 2.05 (s, 3 H), 2.02 (s, 3 H), 0.93–0.87 (m, 2H), 0.00 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.5, 169.8, 129.4, 125.8, 90.2, 77.1, 68.9, 65.5, 64.9, 31.9, 24.5, 21.0, 20.7, 18.0, –1.5; MS m/z molecular ion too fleeting to be accurately mass measured.

For the minor diastereomer: IR (neat, cm^{-1}) 1745, 1640, 1370, 1250, 1040; ^1H NMR (300 MHz, $CDCl_3$) δ 6.13–6.12 (m, 1 H), 5.03 (dd, J = 11.1, 3.5 Hz, 1 H), 4.85 (ABq, J = 7.5 Hz, $\Delta\nu$ = 35.6 Hz, 2 H), 4.15 (s, 2 H), 3.76–3.67 (m, 1 H), 3.62–3.53 (m, 1 H), 2.68–2.61 (m, 2 H), 2.20–2.10 (m, 1 H), 2.09 (s, 3 H), 2.05 (s, 3 H), 1.91–1.82 (m, 1 H), 0.96–0.90 (m, 2 H), 0.02 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.39, 170.36, 129.6, 127.7, 90.9, 76.5, 70.1, 65.5, 65.4, 34.3, 24.4, 21.2, 20.8, 18.1, –1.5. Anal. Calcd for $C_{17}H_{29}BrO_6Si$: C, 46.68; H, 6.68. Found: C, 46.97; H, 6.73.

(±)-*trans*-3-Bromo-6-hydroxy-1-(methoxymethoxy)-2-cyclohexene-1-methanol Diacetate (11b). To a solution of **9** (635 mg, 2.07 mmol) in CH_2Cl_2 (5 mL) was added MOMCl (0.50 mL, 6.6 mmol) and diisopropylethylamine (1.8 mL, 10.3 mmol) under an atmosphere of N_2. After 21 h of reflux, the cooled

reaction mixture was poured into 5% HCl (40 mL) and extracted with CH_2Cl_2 (2 × 25 mL). The combined organic phases were dried and concentrated, and the residue was subjected to flash chromatography (silica gel, elution with 2:1 hexane–ethyl acetate) to give 661 mg (91%) of **11b** as a colorless oil; IR (neat, cm^{-1}) 1750, 1650, 1450, 1375, 1250, 930; ^1H NMR (300 MHz, $CDCl_3$) δ 5.97 (s, 1 H), 5.13 (dd, J = 6.3, 2.6 Hz, 1 H), 4.72 (ABq, J = 7.5 Hz, $\Delta\nu$ = 39.3 Hz, 2 H), 4.21 (ABq, J = 11.8 Hz, $\Delta\nu$ = 43.0 Hz, 2 H), 3.33 (s, 3 H), 2.54–2.49 (m, 2 H), 2.13–1.89 (m, 2 H), 2.04 (s, 3 H), 2.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.5, 169.7, 129.5, 125.6, 92.0, 77.2, 69.0, 65.1, 55.5, 31.9, 24.4, 20.9, 20.7; FAB MS m/z (M^+ + 1) calcd 351.05, obsd 351.11. Anal. Calcd for $C_{13}H_{19}BrO_6$: C, 44.77; H, 5.45. Found: C, 44.53; H, 5.53.

(±)-*trans*-3-Bromo-6-hydroxy-1-[[2-(trimethylsilyl)ethoxy]methoxy]-2-cyclohexene-1-methanol 1-*p*-Toluenesulfonate (12a). A solution of **11a** (1.156 g, 2.64 mmol) in THF–methanol (1:1, 30 mL) was treated with NaOH (5.6 mL of 1.0 M, 5.6 mmol) at 0 °C, stirred for 10 min, and concentrated in vacuo. The residue was taken up in 5% HCl (40 mL) and the product was extracted into ether (2 × 50 mL). The combined organic phases were dried and concentrated. Purification of the residue by flash chromatography (silica gel, gradient elution with 2:1 to 1:2 hexane–ethyl acetate) gave the diol as a colorless oil (855 mg, 92%): IR (neat, cm^{-1}) 3420, 1645, 1255, 1105, 1060, 1030; ^1H NMR (300 MHz, $CDCl_3$) δ 5.92–5.91 (m, 1 H), 4.80 (ABq, J = 7.5 Hz, $\Delta\nu$ = 25.9 Hz, 2 H), 4.00 (dd, J = 7.7, 3.1 Hz, 1 H), 3.86–3.50 (m, 4 H), 3.17 (br s, 2 H), 2.66–2.44 (m, 2 H), 2.11–2.01 (m, 1 H), 1.93–1.82 (m, 1 H), 0.93 (t, J = 8.5 Hz, 2 H), 0.01 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 128.7, 127.0, 89.9, 80.3, 69.3, 65.9, 64.9, 32.6, 27.6, 18.2, −1.5. Anal. Calcd for $C_{13}H_{25}BrO_4Si$: C, 44.19; H, 7.13. Found: C, 44.47; H, 7.14.

A solution of the diol (759 mg, 2.15 mmol) in CH_2Cl_2 (10.0 mL) was cooled to 0 °C under N_2, treated with tosyl chloride (620 mg, 3.3 mmol), triethylamine (0.45 mL, 3.2 mmol), and 4-(dimethylamino)pyridine (7 mg, 0.057 mmol), stirred at rt for 24 h, poured into 5% HCl (30 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried and concentrated, and the residue was subjected to flash chromatography (silica gel, gradient elution with 10:1 to 5:1 hexane–ethyl acetate) to furnish **12a** as a colorless oil (1.01 g, 93%): IR (neat, cm^{-1}) 3500 (br), 1650, 1600, 1370, 1180; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 8.3 Hz, 2 H), 7.35 (d, J = 8.1 Hz, 2 H), 5.80 (d, J = 1.5 Hz, 1 H), 4.71 (ABq, J = 7.9 Hz, $\Delta\nu$ = 25.7 Hz, 2 H), 4.20 (ABq, J = 10.7 Hz, $\Delta\nu$ = 54.1 Hz, 2 H), 3.96 (dd, J = 8.3, 3.0 Hz, 1 H), 3.72–3.53 (m, 2 H), 2.87 (br s, 1 H), 2.63–2.49 (m, 2 H), 2.44 (s, 3 H), 2.04–1.95 (m, 1 H), 1.86–1.76 (m, 1 H), 0.91–0.85 (m, 2 H), 0.01 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 145.1, 132.6, 129.9, 129.3, 128.0, 125.9, 89.9, 79.1, 70.0, 68.2, 65.9, 32.7, 27.0, 21.7, 18.1, −1.5; FAB MS m/z (M^+ + 1) calcd 507.10, obsd 507.17. Anal. Calcd for $C_{20}H_{31}BrO_6SSi$: C, 47.33; H, 6.16. Found: C, 47.09; H, 6.17.

(±)-*trans*-3-Bromo-6-hydroxy-1-(methoxymethoxy)-2-cyclohexene-1-methanol 1-*p*-Toluenesulfonate (12b). A 2.71 g (7.72 mmol) sample of **11b** was saponified as described above to give the diol as a thick, colorless oil (1.57 g, 76%): IR (neat, cm^{-1}) 3425, 1645, 1025; ^1H NMR (300 MHz, $CDCl_3$) δ 5.92 (t, J = 1.7 Hz, 1 H), 4.79 (ABq, J = 7.4 Hz, $\Delta\nu$ = 29.2 Hz, 2 H), 4.06 (dd, J = 8.1, 3.2 Hz, 1 H), 3.81 (ABq, J = 12.3 Hz, $\Delta\nu$ = 44.0 Hz, 2 H), 3.44 (s, 3 H), 2.80 (br s, 2 H), 2.71–2.49 (m, 2 H), 2.13–2.03 (m, 1 H), 1.97–1.86 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 129.0, 126.7, 91.8, 80.3, 69.1, 65.0, 55.6, 32.5, 27.6; FAB MS m/z (M^+ + 1) calcd 267.04, obsd 267.19. Anal. Calcd for $C_9H_{15}BrO_4$: C, 40.47; H, 5.66. Found: C, 40.46; H, 5.84.

Monotosylation of 1.49 g (5.59 mmol) of this material in the predescribed manner afforded 2.14 g (91%) of **12b** as a colorless oil: IR (neat, cm^{-1}) 3540 (br), 1650, 1600, 1360, 1180; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 2 H), 7.36 (d, J = 8.1 Hz, 2 H), 5.80 (d, J = 1.6 Hz, 1 H), 4.68 (ABq, J = 7.6 Hz, $\Delta\nu$ = 46.3 Hz, 2 H), 4.20 (ABq, J = 10.6 Hz, $\Delta\nu$ = 57.2 Hz, 2 H), 3.99 (dd, J = 7.9, 3.0 Hz, 1 H), 3.35 (s, 3 H), 2.67–2.50 (m, 3 H), 2.46 (s, 3 H), 2.06–1.96 (m, 1 H), 1.88–1.79 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 145.1, 132.4, 130.0 (2 C), 128.0, 125.2, 91.9, 79.0, 70.5, 67.8, 55.9, 32.5, 27.0, 21.7; FAB MS m/z (M^+ + 1) calcd 421.04, obsd 421.14. Anal. Calcd for $C_{16}H_{21}O_6S$: C, 45.61; H, 5.02. Found: C, 45.67; H, 5.22.

(±)-[2-[[(*cis*-3-Bromo-7-oxabicyclo[4.2.0]oct-2-en-1-yl)oxy]methoxy]ethyl]trimethylsilane (13a). A solution of **12a** (979 mg, 1.93 mmol) in methanol (10 mL) was treated with K_2CO_3 (407 mg, 2.95 mmol), stirred at rt for 20 h, diluted with water (5 mL), and freed of methanol in vacuo. The product was extracted into ether (2 × 25 mL), dried, and concentrated. The residue was purified by flash chromatography (silica gel, gradient elution with 30:1 to 20:1 hexane–ethyl acetate) to give **13a** as a colorless oil (474 mg, 73%); IR (neat, cm^{-1}) 1640, 1250, 1090, 1020; ^1H NMR (300 MHz, $CDCl_3$) δ 6.15 (d, J = 2.5 Hz, 1 H), 5.04 (s, 1 H), 4.77–4.72 (m, 2 H), 4.62 (d, J = 7.3 Hz, 1 H), 4.19 (d, J = 5.6 Hz, 1 H), 3.84–3.77 (m, 1 H), 3.58–3.49 (m, 1 H), 2.87–2.75 (m, 1 H), 2.50 (dd, J = 17.4, 5.5 Hz, 1 H), 2.04–1.95 (m, 1 H), 1.82–1.70 (m, 1 H), 0.97–0.83 (m, 2 H), 0.03 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 128.1, 127.1, 91.1, 85.1, 80.7, 75.1, 65.7, 30.2, 25.0, 18.1, −1.4; MS m/z ($M^+ - OCH_2OCH_2CH_2SiMe_3$) calcd 186.9793, obsd 186.9758. Anal. Calcd for $C_{13}H_{23}BrO_3Si$: C, 46.57; H, 6.91. Found: C, 46.89; H, 6.97.

(±)-*cis*-3-Bromo-1-(methoxymethoxy)-7-oxabicyclo[4.2.0]oct-2-ene (13b). A solution of **12b** (4.02 g, 9.54 mmol) in methanol (75 mL) was treated with K_2CO_3 (1.95 g, 14.1 mmol), stirred overnight at rt, and worked up as described above. There was obtained 1.93 g (81%) of **13b** as a colorless oil: IR (neat, cm^{-1}) 1650, 1360, 1150, 1025; ^1H NMR (300 MHz, $CDCl_3$) δ 6.14 (d, J = 2.6 Hz, 1 H), 5.03 (s, 1 H), 4.76 (d, J = 7.1 Hz, 1 H), 4.73 (d, J = 5.7 Hz, 1 H), 4.53 (d, J = 7.1 Hz, 1 H), 4.19 (d, J = 5.7 Hz, 1 H), 3.40 (s, 3 H), 2.86–2.74 (m, 1 H), 2.53–2.45 (m, 1 H), 2.03–1.94 (m, 1 H), 1.77–1.65 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 127.9, 127.2, 92.9, 85.0, 80.6, 75.2, 55.8, 30.2, 24.9; FAB MS m/z (M^+ + 1) calcd 249.01, obsd 249.09. Anal. Calcd for $C_9H_{13}BrO_3$: C, 43.39; H, 5.26. Found: C, 43.43; H, 5.35.

(±)-2-[*cis*-1-(Methoxymethoxy)-7-oxabicyclo[4.2.0]oct-2-en-3-yl]-2-adamantanol (15). A THF solution (5 mL) of **13b** (161 mg, 0.646 mmol) was cooled to −78 °C under N_2, admixed with *tert*-butyllithium (0.80 mL of 1.7 M in pentane, 1.36 mmol), stirred at −78 °C for 6 min, and treated with a THF solution (3 mL) of 2-adamantanone (82 mg, 0.547 mmol) via cannula. The reaction mixture was maintained at −78 °C for 15 min, quenched with saturated NH_4Cl solution (5 mL), warmed to rt, diluted with water (25 mL), and extracted with ether (2 × 30 mL). The combined organic layers were dried and concentrated to leave a residue that was purified by flash chromatography (silica gel, gradient elution with 2:1 to 1:1 hexane–ethyl acetate). There was isolated 128 mg (73%) of **15**, a white solid, mp 97–98 °C; IR ($CHCl_3$, cm^{-1}) 3600, 3020, 1455, 1160, 1125, 1030; ^1H NMR (300 MHz, C_6D_6) δ 5.74 (s, 1 H), 5.14 (s, 1 H), 4.89 (d, J = 5.6 Hz, 1 H), 4.64 (d, J = 7.1 Hz, 1 H), 4.37 (d, J = 7.1 Hz, 1 H), 4.13 (d, J = 5.5 Hz, 1H), 3.12 (s, 3 H), 2.47 (br d, J = 12.3 Hz, 2 H), 2.39–2.20 (m, 2 H), 2.08 (br d, J = 9.4 Hz, 2 H), 2.01–1.93 (m, 1 H), 1.88–1.51 (br m, 11H), 1.41–1.30 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 147.3, 122.4, 92.9, 86.6, 81.9, 75.7, 73.9, 55.3, 38.0, 35.7, 35.0 (2 C), 34.6, 33.4, 32.8, 27.8, 27.7, 25.2, 18.5; MS m/z (M^+) calcd 320.1987, obsd 320.1975. Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.22; H, 8.90.

(±)-*cis*-1-(Methoxymethoxy)-7-oxabicyclo[4.2.0]oct-2-en-3-yl Phenyl Ketone (17). A THF solution (6 mL) of **13b** (241 mg, 0.966 mmol) was cooled to −78 °C under N_2, admixed with *tert*-butyllithium (1.2 mL of 1.7 M in pentane, 2.0 mmol), stirred at −78 °C for 6 min, treated with a THF solution (3 mL) of benzaldehyde (84 mg, 0.79 mmol), and worked up in the predescribed manner to give 169 mg (77%) of **16** as a colorless oil; IR (neat, cm^{-1}) 3430, 1455, 1025; MS m/z (M^+) calcd 276.1361, obsd 276.1316.

A benzene solution (3 mL) of **16** (12 mg, 0.045 mmol) containing MnO_2 (48 mg, 0.552 mmol) was vigorously stirred at rt for 2 h, treated with additional MnO_2 (40 mg, 0.46 mmol), stirred for an additional 2 h, filtered through a pad of Celite which was subsequently rinsed several times with ether, and concentrated. Flash chromatography of the residue (silica gel, gradient elution with 10:1 to 5:1 hexane–ethyl acetate) provided **17** as a white

solid (10 mg, 81%): mp 72–74 °C; IR (film, cm^{-1}) 1650, 1270, 1250, 1020; ^1H NMR (300 MHz, C_6D_6) δ 7.76–7.72 (m, 2 H), 7.13–7.03 (m, 3 H), 6.38 (t, J = 1.2 Hz, 1 H), 5.06 (s, 1 H), 4.73 (d, J = 5.9 Hz, 1 H), 4.39 (d, J = 7.3 Hz, 1 H), 4.22 (d, J = 7.2 Hz, 1 H), 3.95 (d, J = 5.8 Hz, 1 H), 3.01 (s, 3 H), 2.81–2.61 (m, 2 H), 1.91–1.83 (m, 1 H), 1.29–1.18 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 195.9, 142.1, 139.1, 138.2, 131.9, 129.8, 128.4, 93.1, 86.1, 80.6, 73.8, 55.3, 24.1, 19.8; MS m/z (M^+) calcd 274.1205, obsd 274.1183. Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.07; H, 6.79.

(±)-(1*R,2*S**,4*R**)-7,7-Dimethoxy-2-[9[1*R**,6*S**)-1-(methoxymethoxy)-7-oxabicyclo[4.2.0]oct-2-en-3-yl]-5-norbornen-2-ol (20).** A dry 50-mL 1-necked flash containing $CeCl_3 \cdot 7H_2O$ (506 mg, 1.36 mmol) was evacuated to <0.1 Torr and heated to 100 °C during 2 h with constant stirring of the solid with a Teflon-coated magnetic stir bar. The temperature was increased to 140 °C during the next hour and maintained at this point for an additional 5 h. The flash was allowed to cool to 25 °C during the next hour, at which time a N_2 atmosphere was established. The flask was placed in an ice bath and the dry $CeCl_3$ powder was suspended in anhydrous THF (7 mL). The mixture was stirred vigorously at rt overnight, titrated with *tert*-butyllithium (ca. 0.3 mL of 1.7 M in pentane) until a permanent orange color was seen, and cooled to −78 °C.

A THF solution (4 mL) of **12b** (122 mg, 0.492 mmol) under N_2 was cooled to −78 °C, treated with *tert*-butyllithium (0.65 mL of 1.7 M in pentane, 1.1 mmol), stirred for 7 min, and transferred via cannula to the $CeCl_3$ slurry. The resulting yellow-orange mixture was stirred at −78 °C for 6 h, treated with **19** (77 mg, 0.457 mmol) dissolved in THF (2 mL) precooled to −78 °C, allowed to warm to room temperature, and stirred overnight. Saturated NH_4Cl solution (5 mL) and ether (10 mL) were introduced, and the mixture was stirred for 30 min prior to decantation from the cerium salts. After dilution with water (25 mL), the products were extracted into ether (2 × 25 mL), and the combined organic phases were dried and concentrated. Purification of the residue by flash chromatography on silica gel (gradient elution with 2:1 to 1:1 hexane–ethyl acetate) gave a 10:1 mixture of **20** and **21** as a colorless oil (61 mg, 40%); IR (neat, cm^{-1}) 3500, 1450, 1400, 1360, 1295, 1225, 1130, 1070, 1025, 965, 925. For the major alcohol: ^1H NMR (300 MHz, C_6D_6) δ 5.85–5.82 (m, 1 H), 5.72 (dd, J = 6.0, 3.4 Hz, 1 H), 5.52 (d, J = 2.0 Hz, 1 H), 5.20 (br s, 1 H), 4.91 (d, J = 5.4 Hz, 1 H), 4.68 (d, J = 6.9 Hz, 1 H), 4.47 (s, 1 H), 4.39 (d, J = 6.9 Hz, 1 H), 4.12 (d, J = 5.4 Hz, 1 H), 3.14 (s, 3 H), 2.93 (s, 3 H), 2.90 (s, 3 H), 2.85–2.82 (m, 1 H), 2.79–2.77 (m, 1 H), 2.64 (br s, 1 H), 2.35–2.23 (m, 1 H), 2.02–1.94 (m, 1 H), 1.90 (d, J = 13.0 Hz, 1 H), 1.65 (dd, J = 13.0, 3.6 Hz, 1 H), 1.59–1.47 (m, 1 H); ^{13}C NMR (62.5 MHz, C_6D_6) ppm 146.1, 135.6, 130.6, 123.2, 120.6, 92.8, 86.4, 81.9, 81.6, 73.8, 55.0, 54.1, 51.8, 48.8, 45.5, 36.4, 24.5, 20.1; MS m/z (M^+) calcd 338.1729, obsd 338.1742. Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.89, H, 7.74. Found: C, 64.22; H, 7.87.

Addition of 18a to 22. Arrival at the Diastereomeric Alcohols 23a and 24a. A 677 mg (1.819 mmol) sample of $CeCl_3 \cdot 7H_2O$, dried in the predescribed manner, was suspended in anhydrous THF (10 mL), titrated to an orange color with *tert*-butyllithium, and treated with the vinyllithium reagent prepared as above from **13a** (303 mg, 0.903 mmol) and *tert*-butyllithium (1.30 mL of 1.7 M, 2.2 mmol). After the addition of **22** (97 mg, 0.592 mmol) for a comparable reaction time, workup and flash chromatographic purification (silica gel, gradient elution 10:1 to 2:1 hexane–ethyl acetate) afforded 109 mg (44%) of the less-polar alcohol and 72 mg (29%) of the more-polar diastereomer.

For the less polar diastereomer: colorless oil: IR (neat, cm^{-1}) 3450, 1255, 1025; ^1H NMR (300 MHz, $CDCl_3$) δ 6.24 (dd, J = 17.8, 11.1 Hz, 1 H), 5.79 (d, J = 2.0 Hz, 1 H), 5.17 (dd, J = 11.1, 1.9 Hz, 1 H), 5.03–4.97 (m, 2 H), 4.75 (d, J = 5.8 Hz, 1 H), 4.64 (ABq, J = 7.2 Hz, Δν = 44.0 Hz, 2 H), 4.09 (d, J = 5.7 Hz, 1 H), 3.82–3.73 (m, 1 H), 3.55–3.42 (m, 1 H), 2.40–2.33 (m, 1 H), 2.22–2.05 (m, 2 H), 1.98–1.64 (m, 6 H), 1.35–1.02 (m, 3 H), 1.22 (s, 3 H), 0.96–0.78 (m, 2 H), 0.74 (s, 3 H), −0.01 (s, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) ppm 148.5, 136.8, 121.0, 115.6, 90.8, 86.3, 84.7, 81.9, 73.2, 65.4, 58.9, 51.1, 45.8, 41.5, 26.0, 25.4, 24.5, 21.6, 21.0, 20.9, 18.0, −1.5; FAB MS m/z (M^+ + 1) calcd 421.28, obsd 421.36. Anal. Calcd for $C_{24}H_{40}O_4Si$: C, 68.53; H, 9.58. Found: C, 68.04; H, 9.67.

For the more polar diastereomer: colorless oil; IR (neat, cm^{-1}) 3440, 1635, 1250, 1020; ^1H NMR (300 MHz, $CDCl_3$) δ 6.31 (dd, J = 17.8, 11.1 Hz, 1 H), 5.83 (d, J = 2.0 Hz, 1 H), 5.20 (dd, J = 11.0, 2.0 Hz, 1 H), 5.05–4.99 (m, 2 H), 4.75 (d, J = 5.7 Hz, 1 H), 4.63 (ABq, J = 7.1 Hz, Δν = 22.6 Hz, 2 H), 4.14 (d, J = 5.7 Hz, 1 H), 3.84–3.75 (m, 1 H), 3.57–3.48 (m, 1 H), 2.53–2.45 (m, 1 H), 2.26–1.99 (m, 4 H), 1.90–1.69 (m, 4 H), 1.41–1.29 (m, 1 H), 1.24 (s, 3 H), 1.21–1.02 (m, 2 H), 0.99–0.80 (m, 2 H), 0.76 (s, 3 H), 0.01 (s, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) ppm 148.1, 137.6, 121.6, 115.4, 91.0, 86.9, 85.6, 81.8, 73.4, 65.5, 58.4, 51.5, 45.6, 42.5, 26.0, 25.7, 24.0, 21.6, 21.1, 20.7, 18.0, −1.5; FAB MS m/z (M^+ + 1) calcd 421.28, obsd 421.38. Anal. Calcd for $C_{24}H_{40}O_4Si$: C, 68.53; H, 9.58. Found: C, 67.93; H, 9.57.

Addition of 18b to 22. Preparation of the Diastereomeric Alcohols 23b and 24b. A 500-mg (1.34 mmol) sample of $CeCl_3 \cdot 7H_2O$, dried in the predescribed manner, was suspended in anhydrous THF (8 mL), titrated to an orange color with *tert*-butyllithium, and treated with the vinyllithium reagent prepared as above from **13b** (193 mg, 0.775 mmol) and *tert*-butyllithium (1.0 mL of 1.7 M in pentane, 1.70 mmol). After the addition of **22** (117 mg, 0.714 mmol) for a comparable reaction time, workup, and flash chromatography (silica gel, gradient elution with 10:1 to 3:1 hexane-ethyl acetate), **23b** and **24b** were obtained as an inseparable mixture of diastereomers: colorless oil; 1:1 ratio, 190 mg (80%); IR (neat, cm^{-1}) 3440, 1630, 1450, 1390, 1370, 1020; ^1H NMR (300 MHz, C_6D_6) δ 6.51–6.38 (m, 1 H), 5.77 (t, J = 2.7 Hz, 1 H), 5.20–5.11 (m, 2 H), 5.03–4.93 (m, 1 H), 4.90–4.87 (m, 1 H), 4.70 (d, J = 7.1 Hz, 0.5 H), 4.62 (d, J = 7.1 Hz, 0.5 H), 4.37 (dd, J = 7.0, 5.4 Hz, 1 H), 4.13 (dd, J = 9.1, 5.5 Hz, 1 H), 3.14 (s, 1.5 H, 3.12 (s, 1.5 H), 2.58–2.22 (m, 2 H), 2.07–1.53 (m, 7 H), 1.38 (s, 1.5 H), 1.37 (s, 1.5 H), 1.35–0.91 (m, 3 H), 0.79 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 149.0, 148.6, 138.4, 137.6, 121.8, 121.4, 115.5, 114.9, 93.0, 92.9, 87.0, 86.4, 85.5, 81.9, 81.8, 74.0, 73.9, 59.3, 58.7, 55.3, 51.8, 51.5, 46.3, 46.2, 42.9, 41.8, 26.3, 25.6, 24.9, 24.5, 22.0, 21.6, 21.4, 21.3, 21.2; MS m/z (M^+) calcd 334.2144, obsd 334.2140.

Anionic Oxy-Cope Rearrangement of 20. A solution of **20** (17 mg, 0.050 mmol) and 18-crown-6 (37 mg, 0.139 mmol) in dry THF (2 mL) under N_2 was treated with potassium hexamethyldisilazide (0.30 mL of 0.5 M in toluene, 0.15 mmol). WIthin a few min, **20** was completely consumed as judged by TLC analysis. The reaction mixture was quenched with saturated NH_4Cl solution, warmed to rt, diluted with water (5 mL), and extracted with ether (2 × 10 mL). The combined organic phases were dried and concentrated to leave a residue that was purified by flash chromatography (silica gel, gradient elution with 3:1 to 1:1 hexane–ethyl acetate) to give 13 mg (80%) of **27** as a colorless oil; IR (neat, cm^{-1}) 1720, 1465, 1370, 1345, 1265, 1160, 1050; ^1H NMR (300 MHz, C_6D_6) δ 5.83 (dd, J = 6.0, 1.7 Hz, 1 H), 5.44 (dd, J = 6.0, 2.6 Hz, 1 H), 4.91 (d, J = 7.4 Hz, 1 H), 4.79 (br s, 1 H), 4.66–4.61 (m, 2 H), 4.56 (d, J = 8.1 Hz, 1 H), 3.34–3.27 (m, 1 H), 3.16 (s, 3 H), 2.93 (s, 3 H), 2.92 (s, 3 H), 2.78–2.70 (m, 1 H), 2.65 (dd, J = 17.3, 2.4 Hz, 1 H), 2.51 (ddd, J = 13.8, 10.9, 2.7 Hz, 1 H), 2.40 (ddd, J = 9.3, 6.9, 2.5 Hz, 1 H), 2.14–1.99 (m, 2 H), 1.89 (dd, J = 14.1, 6.5 Hz, 1 H), 1.66–1.57 (m, 1 H), 1.34–1.22 (m, 1 H); ^{13}C NMR (62.5 MHz, C_6D_6) ppm 208.4, 135.0, 133.2, 112.4, 91.8, 86.0, 81.1, 75.9, 55.5, 49.2, 48.4, 43.2, 41.2, 41.1, 37.6, 37.1, 26.2, 13.3; MS m/z (M^+) calcd 338.1729, obsd 338.1724.

Base-Induced Degradation of 23a and 24a. A solution of the lower polarity diastereomer (26 mg, 0.062 mmol) in anhydrous THF (1.5 mL) containing 18-crown-6 (79 mg, 0.299 mmol) was transferred via cannula to a magnetically stirred suspension of KH (16 mg, 0.405 mmol, pretreated with iodine) in THF (0.5 mL) at 0 °C. The reaction mixture was maintained under N_2 at 0 °C for 30 min, warmed to rt for 2 h, quenched with saturated NH_4Cl solution (0.5 mL), diluted with water (5 mL), and extracted with ether (2 × 10 mL). The combined organic phases were dried and concentrated, and the residue was purified by flash chromatography (silica gel, elution with 10:1 hexane–ethyl acetate) to give **28** as a colorless oil (6 mg, 32%). The several more polar byproducts, which also lacked the trimethylsilyl group, were not examined further.

For **28**: IR (neat, cm^{-1}) 3500 (br), 1635, 1610, 1585, 1490; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23–7.12 (m, 3 H), 6.95–6.92 (m, 1 H), 6.34 (dd, J = 17.8, 11.0 Hz, 1 H), 5.30 (dd, J = 11.0, 2.0 Hz, 1 H), 5.20 (ABq, J = 6.8 Hz, Δν = 6.5 Hz, 2 H), 4.86 (dd, J = 17.8, 2.0 Hz, 1 H), 3.72 (q, J = 7.1 Hz, 2 H), 2.41 (d, J = 13.8 Hz, 1 H),

2.28 (dt, J = 13.8, 3.7 Hz, 1 H), 1.96 (t, J = 4.3 Hz, 1 H), 1.90 (br s, 1 H), 1.79–1.67 (m, 1 H), 1.62–1.52 (m, 2 H), 1.36 (s, 3 H), 1.26–1.20 (m, 1 H), 1.22 (t, J = 7.1 Hz, 3 H), 0.84 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 156.9, 147.7, 136.0, 128.5, 120.1, 117.3, 115.3, 114.8, 93.4, 84.5, 64.2, 60.0, 51.5, 46.1, 44.5, 26.4, 26.0, 21.8, 21.4, 15.1; MS m/z (M^+) calcd 316.2038, obsd 316.2042.

Base-Induced Degradation of 23b/24b. To a cold (0 °C), magnetically stirred solution of **23b/24b** (19 mg, 0.057 mmol) and 18-crown-6 (15 mg, 0.056 mmol) in THF (1.3 mL) under N_2 was added potassium hexamethyldisilazide (0.30 mL of 0.50 M in toluene, 0.15 mmol) via syringe. After 10 min, the reaction mixture was warmed to rt, stirred for 1.5 h, quenched with saturated NH_4Cl solution (2 mL), diluted with water (2 mL), and extracted with ether (2 × 5 mL). After the combined organic layers were dried and concentrated, the residue was subjected to flash chromatography (silica gel, gradient elution with 10:1 to 1:1 hexane–ethyl acetate). There wasobtained 5 mg (26%) of **29** along with more-polar products not yet characterized.

The use of KH in the predescribed manner furnished **29** in 19% yield.

For **29**: colorless oil; IR (neat, cm^{-1}) 3500 (br), 1635, 1605, 1580; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23–7.13 (m, 3 H), 6.95–6.91 (m, 1 H), 6.35 (dd, J = 17.8, 11.0 Hz, 1 H), 5.31 (dd, J = 11.0, 2.0 Hz, 1 H), 5.15 (ABq, J = 6.7 Hz, $\Delta\nu$ = 6.9 Hz, 2 H), 4.85 (dd, J = 17.8, 2.0 Hz, 1 H), 3.47 (s, 3 H), 2.41 (d, J = 13.8 Hz, 1 H), 2.28 (dt, J = 13.8, 3.6 Hz, 1 H), 1.96 (t, J = 4.3 Hz, 1 H), 1.89 (br s, 1 H), 1.78–1.67 (m, 1 H), 1.62–1.52 (m, 1 H), 1.36 (s, 3 H), 1.26–1.16 (m, 1 H), 0.87–0.75 (m, 1 H), 0.84 (s, 3 H); MS m/z (M^+) calcd 302.1882, obsd 302.1882.

Thermal Activation of 23a. A decalin solution (1 mL) of the lower polarity diastereomeric alcohol (21 mg, 0.050 mmol) was deoxygenated with bubbling N_2 for 20 min, blanketed with N_2, refluxed for 5 h, and cooled to rt. The solution was poured onto a column of silica gel and the decalin was removed by elution with 50:1 hexane–ethyl acetate. A polarity increase to 5:1 hexane–ethyl acetate caused **32** to elute as a colorless oil (10 mg, 47%).

Comparable treatment of the more-polar diastereomer (9 mg, 0.021 mmol) furnished **33** as a colorless oil (5 mg, 56%).

For **32** (relative stereochemistry unknown): IR (neat, cm^{-1}) 1675, 1250, 1075, 1020; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (d, J = 2.3 Hz, 1 H), 5.27 (qt, J = 7.3, 2.1 Hz, 1 H), 5.16 (br s, 1 H), 4.84 (d, J = 6.0 Hz, 1 H), 4.72 (ABq, J = 7.4 Hz, $\Delta\nu$ = 14.1 Hz, 2 H), 4.19 (d, J = 5.9 Hz, 1 H), 3.83–3.74 (m, 1 H), 3.65–3.56 (m, 1 H), 2.80–2.71 (m, 2 H), 2.60–2.52 (m, 1 H), 2.33–2.20 (m, 3 H), 2.14–2.02 (m, 2 H), 1.79–1.73 (m, 1 H), 1.70 (dt, J = 7.3, 2.0 Hz, 3 H), 1.46–1.35 (m, 2 H), 1.25 (s, 3 H), 0.99 (s, 3 H), 0.95–0.88 (m, 2 H), 0.03 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 200.5, 150.0, 142.8, 136.6, 115.5, 91.5, 86.3, 80.8, 73.6, 65.9, 48.8, 42.8, 37.5, 33.6, 29.3, 26.3, 23.8, 21.4, 18.2, 17.9, 13.6, –1.4; FAB MS m/z (M^+ + 1) calcd 421.28, obsd 421.40.

For **33** (relative stereochemistry unknown): IR (neat, cm^{-1}) 1675, 1250, 1080, 1020, 860, 840; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (d, J = 2.4 Hz, 1 H), 5.27 (qt, J = 7.3, 2.0 Hz, 1 H), 5.16 (br s, 1 H), 4.84 (d, J = 6.0 Hz, 1 H), 4.72 (ABq, J = 7.4 Hz, $\Delta\nu$ = 14.0 Hz, 2 H), 4.19 (d, J = 6.0 Hz, 1 H), 3.84–3.75 (m, 1 H), 3.65–3.56 (m, 1 H), 2.78–2.68 (m, 2 H), 2.62–2.54 (m, 1 H), 2.35–2.22 (m, 3 H), 2.12–2.02 (m, 2 H), 1.80–1.72 (m, 1 H), 1.70 (dt, J = 7.3, 2.0 Hz, 3 H), 1.47–1.36 (m, 2 H), 1.25 (s, 3 H), 0.99 (s, 3 H), 0.95–0.88 (m, 2 H), 0.03 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 200.6, 150.0, 142.8, 136.7, 115.5, 91.4, 86.3, 80.8, 73.6, 65.9, 49.0, 42.8, 37.4, 33.6, 29.3, 26.3, 23.7, 21.4, 18.2, 17.9, 13.6, –1.4; FAB MS m/z (M^+ + 1) calcd 421.28, obsd 421.43.

(±)-*trans*-1-(Benzyloxy)-3-bromo-6-hydroxy-2-cyclohexene-1-methanol Diacetate and (±)-*cis*-1-(Benzyloxy)-3-bromo-6-hydroxy-2-cyclohexene-1-methanol Diacetate (34 and 35). To a suspension of sodium hydride (468 mg of 60% oil dispersion, 11.7 mmol, washed with pentane (3 × 5 mL)) in dry DMF (10 mL) at 0 °C was added tetra-*n*-butylammonium iodide (277 mg, 0.750 mmol) and benzyl bromide (1.0 mL, 8.4 mmol). The resulting mixture was treated dropwise with a DMF solution (10 mL) of **9/10** (2.35 g, 7.65 mmol, 5:1 diastereomer mixture), stirred for 20 h at 0 °C, treated with saturated NH_4Cl solution (10 mL), poured into 5% HCl (80 mL), and extracted with ether (2 × 75 mL). The combined organic phases were dried and concentrated, and the residue was purified by flash chromatography (silica gel, elution with 5:1 hexane–ethyl acetate) to give 2.53 g (83%) of product mixture as a faintly yellow oil. The diastereomers were separated by MPLC (silica gel, elution with 3:1 hexane–ethyl acetate) with the major isomer **34** being less polar than **35**.

F5o **34**: colorless oil; IR (neat, cm^{-1}) 1750, 1375, 1250, 1060; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.23 (m, 5 H), 6.04 (s, 1 H), 5.26 (dd, J = 7.0, 2.9 Hz, 1H), 4.53 (ABq, J = 11.2 Hz, $\Delta\nu$ = 5.6 Hz, 2 H), 4.28 (ABq, J = 11.9 Hz, $\Delta\nu$ = 33.2 Hz, 2 H), 2.59–2.54 (m, 2 H), 2.20–1.97 (m, 2 H), 2.06 (s, 3 H), 2.05 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.5, 169.7, 138.2, 129.2, 128.2, 127.5, 127.3, 126.5, 77.2, 68.3, 65.2, 63.7, 32.2, 24.9, 20.9, 20.6; FAB MS m/z (M^+ + 1) calcd 397.07, obsd 397.20. Anal. Calcd for $C_{18}H_{21}BrO_4$: C, 54.42; H, 5.33. Found: C, 54.50; H, 5.45.

For **35**: colorless oil; IR (neat, cm^{-1}) 1750, 1650, 1375, 1240, 1050; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.23 (m, 5H), 6.11 (t, J = 1.6 Hz, 1 H), 5.09 (dd, J = 10.6, 3.5 Hz, 1 H), 4.68 (ABq, J = 11.7 Hz, $\Delta\nu$ = 8.6 Hz, 2 H), 4.18 (ABq, J = 11.5 Hz, $\Delta\nu$ = 32.1 Hz, 2 H), 2.67–2.62 (m, 2 H), 2.29–2.13 (m, 1 H), 2.07 (s, 3 H), 2.06 (s, 3 H), 1.96–1.87 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.5, 170.4, 138.9, 129.3, 128.3, 127.7, 127.5, 127.1, 76.1, 70.4, 66.9, 65.1, 34.0, 24.9, 21.2, 20.8; FAB MS m/z (M^+ + 1) calcd 397.07, obsd 397.10.

(±)-*cis*-4a-(Benzyloxy)-6-bromo-4a,7,8,8a-tetrahydro-2,2-dimethyl-1,3-benzodioxan and (±)-*trans*-4a-(Benzyloxy)-6-bromo-4a,7,8,8a-tetrahydro-2,2-dimethyl-1,3-benzodioxan (36 and 37). A solution of the **34/35** mixture (1.007 g, 2.53 mmol) in THF and methanol (1:1, 20 mL) was cooled to 0 °C and treated with NaOH (5.3 mL of 1.0 N, 5.3 mmol). After 10 min, the mixture was concentrated in vacuo, the residue was diluted with ethyl acetate (20 mL) and extracted with 5% HCl (35 mL), and the aqueous layers were reextracted with ethyl acetate (2 × 30 mL). The combined organic phases were dried and concentrated in vacuo, and the resulting white solid was dried by concentration from benzene (3 × 20 mL) prior to being suspended in acetone (25 mL) and treated with 2,2-dimethoxypropane (1.0 mL, 8.1 mmol) in addition to pyridinium *p*-toluenesulfonate (78 mg, 0.309 mmol). Within 10 min, the mixture became clear and homogeneous. After 8 h, the solution was concentrated, diluted with saturated $NaHCO_3$ solution (50 mL), and extracted with ether (2 × 50 mL). The combined organic phases were dried and concentrated to leave a residue that was purified by flash chromatography on silica gel (elution with 10:1 hexane–ethyl acetate) to give the less polar isomer **36** (594 mg, 66%) and the more polar **37** (108 mg, 12%).

For **36**: colorless solid, mp 62–64 °C; IR ($CHCl_3$, cm^{-1}) 1650, 1380, 1235, 1210, 1115, 1080; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.25 (m, 5 H), 6.08 (t, J = 0.9 Hz, 1 H), 4.53 (ABq, J = 11.1 Hz, $\Delta\nu$ = 26.7 Hz, 2 H), 4.04 (t, J = 1.5 Hz, 1 H), 3.84 (ABq, J = 11.6 Hz, $\Delta\nu$ = 36.2 Hz, 2 H), 2.72 (dddd, J = 17.8, 11.6, 6.0, 2.3 Hz, 1 H), 2.39 (dd, J = 17.9, 6.2 Hz, 1 H), 2.23–2.12 (m, 1 H), 1.87–1.79 (m, 1 H), 1.48 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 138.7, 130.2, 128.4, 127.6, 127.4, 127.3, 98.6, 71.6, 67.8, 67.2, 65.6, 30.8, 27.8, 25.5, 19.9; FAB MS m/z (M^+ + 1) calcd 353.08, obsd 353.10. Anal. Calcd for $C_{17}H_{21}BrO_3$: C, 57.80; H, 5.99. Found: C, 58.01; H, 6.10.

For **37**: white solid, mp 85–89 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.23 (m, 5 H), 5.91 (t, J = 1.6 Hz, 1 H), 4.68 (d, J = 11.4 Hz, 1 H), 4.55 (d, J = 11.4 Hz, 1 H), 4.07 (d, J = 12.5 Hz, 1 H), 3.92 (dd, J = 12.3, 3.7 Hz, 1 H), 3.68 (d, J = 12.5 Hz, 1 H), 2.70–2.65 (m, 2 H), 2.48–2.37 (m, 1 H), 1.71–1.64 (m, 1 H), 1.50 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 139.2, 130.7, 128.1, 127.3, 127.1, 126.7, 99.3, 71.3, 69.3, 64.7, 62.9, 35.4, 29.4, 23.7, 18.8.

(1*S*,2*S*,4*R*)-2-[(4a*S*,8a*R*)-4a-(Benzyloxy)-4a,7,8,8a-tetrahydro-2,2-dimethyl-1,3-benzodioxan-6-yl]-7,7-dimethyl-1-vinyl-2-norbornanol and (1*S*,2*S*,4*R*)-2-[(4a*R*,8a*S*)-4a-(Benzyloxy)-4a,7,8,8a-tetrahydro-2,2-dimethyl-1,3-benzodioxan-6-yl]-7,7-dimethyl-1-vinyl-2-norbornanol (39 and 40). (All glassware was base-washed and oven-dried prior to use). A 50-mL one-necked flask containing $CeCl_3 \cdot 7H_2O$ (506 mg, 1.359 mmol) was evacuated to <0.1 Torr and heated to 100 °C over a period of 90 min while constantly stirring the solid with a Teflon stirring bar. Heating was continued to 140 °C over an additional 1 h and maintained at this temperature for 5 h. The flask was allowed to cool to rt during 1 h, at which time an atmosphere of N_2 was established. The flask was placed in an ice bath and the dry

$CeCl_3$ powder was suspended in anhydrous THF (8 mL). The resulting mixture was stirred vigorously at rt for 11 h, titrated with *tert*-butyllithium until a permanent orange color developed to assure dryness, and cooled to −78 °C.

A THF solution (5 mL) of **36** (249 mg, 0.706 mmol) under N_2 was cooled to −78 °C, treated with *tert*-butyllithium (0.90 mL of 1.7 M in pentane, 1.5 mmol), stirred at −78 °C for 10 min, and transferred via cannula to the $CeCl_3$ slurry. The dark-orange mixture was stirred at −78 °C for 4 h, treated with **22** (96 mg, 0.585 mmol) dissolved in THF (4 mL), and continuously agitated a further 4.5 h before being warmed to rt and quenched with saturated NH_4Cl solution. After being stirred for 30 min, the solution was decanted, diluted with water (50 mL), and extracted with ether (2 × 50 mL). The combined organic extracts were dried and concentrated to leave a residue that was subjected to flash chromatography on silica gel (gradient elution with 15:1 to 5:1 hexane–ethyl acetate) to give the less-polar **39** (89 mg, 35%) and the more-polar **40** (111 mg, 43%), together with a mixed fraction containing both (27 mg, 10%).

For **39**: colorless oil; IR (neat, cm^{-1}) 3450 (br), 1630, 1450, 1374; ^1H NMR (300 MHz, C_6D_6) δ 7.28 (d, J = 7.1 Hz, 2 H), 7.20–7.06 (m, 3 H), 6.42 (dd, J = 17.9, 11.1 Hz, 1 H), 5.62 (s, 1 H), 5.17 (dd, J = 11.1, 2.1 Hz, 1 H), 5.02 (dd, J = 17.9, 2.1 Hz, 1 H), 4.41 (ABq, J = 11.8 Hz, $\Delta\nu$ = 18.9 Hz, 2 H), 4.05 (s, 1 H), 3.81 (ABq, J = 11.4 Hz, $\Delta\nu$ = 62.0 Hz, 2 H), 2.40–2.28 (m, 1 H), 2.18–2.08 (m, 2 H), 1.91–1.57 (m, 7 H), 1.36 (s, 3 H), 1.35 (s, 3 H), 1.34 (s, 3 H), 1.29–1.05 (m, 2 H), 0.81 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 149.8, 140.4, 137.8, 128.5, 127.52, 127.47, 120.8, 115.2, 98.5, 84.8, 70.0, 69.0, 68.2, 65.6, 59.2, 51.5, 46.3, 41.9, 28.0, 26.4, 24.6, 22.3, 22.0, 21.3, 20.2; FAB MS m/z (M^+ + 1) calcd 439.29, obsd 439.40; $[\alpha]^{23}_D$ =84.3° (c 2.3, $CHCl_3$). Anal. Calcd for $C_{28}H_{38}O_4$: C, 76.68; H, 8.73. Found: C, 76.41; H, 8.88.

For **40**: colorless oil; IR (neat, cm^{-1}) 3450 (br), 1630, 1455, 1380; ^1H NMR (300 MHz, C_6D_6) δ 7.28 (d, J = 7.2 Hz, 2 H), 7.20–7.06 (m, 3 H), 6.41 (dd, J = 17.9, 11.1 Hz, 1 H), 5.73 (s, 1 H), 5.20 (dd, J = 11.1, 2.0 Hz, 1 H), 5.04 (dd, J = 17.9, 2.0 Hz, 1 H), 4.38 (ABq, J = 11.6 Hz, $\Delta\nu$ = 13.8 Hz, 2 H), 4.05 (s, 1 H), 3.81 (ABq, J = 11.5 Hz, $\Delta\nu$ = 57.8 Hz, 2 H), 2.41–2.21 (m, 2 H), 2.06–1.59 (m, 7 H), 1.36 (s, 3 H), 1.34 (s, 3 H), 1.33 (s, 3 H), 1.31–1.20 (m, 1 H), 0.99–0.84 (m, 2 H), 0.78 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 150.0, 140.2, 138.1, 128.5, 127.5, 127.4, 121.8, 115.5, 98.6, 84.8, 70.9, 69.1, 68.1, 65.6, 59.4, 51.5, 46.1, 42.7, 27.8, 26.7, 25.8, 24.9, 22.3, 22.0, 21.3, 20.7; FAB MS m/z (M^+ + 1) calcd 439.29, obsd 439.40; $[\alpha]^{23}_D$ +59.2° (c 1.6, $CHCl_3$). Anal. Calcd for $C_{28}H_{38}O_4$: C, 76.68; H, 8.73. Found: C, 76.37; H, 8.84.

(4a*R*,6a*S*,9*R*,12*E*,14a*R*,14b*S*)-14b-(Benzyloxy)-1,4a,5,6,-6a,8,9,10,11,14,14a,14b-dodecahydro-6a-hydroxy-3,3,15,15-tetramethyl-9,12-methano-7*H*-cyclodeca[*f*][1,3]benzodioxin-7-one (41). Potassium hexamethyldisilazide (0.65 mL of 0.5 M in toluene, 0.33 mmol) was added to a benzene solution (3 mL) of **39** (29 mg, 0.065 mmol) and 18-crown-6 (53 mg, 0.20 mmol) without provision for excluding O_2. The reaction mixture was stirred at rt for 18 h, treated with saturated NH_4Cl solution (1 mL), diluted with water (5 mL), extracted with ether (2 × 15 mL), dried, concentrated, and purified by flash chromatography (silica gel, gradient elution with 10:1 to 5:1 hexane–ethyl acetate) to give 16 mg (53%) of **41** as a white solid, mp 132–135 °C; IR (film, cm^{-1}) 1690, 1450, 1385; ^1H NMR (300 MHz, C_6D_6) δ 7.83 (d, J = 7.4 Hz, 2 H), 7.33 (t, J = 7.6 Hz, 2 H), 7.21–7.10 (m, 1 H), 5.27 (br d, J = 12.7 Hz, 1 H), 4.83 (ABq, J = 12.7 Hz, $\Delta\nu$ = 27.8 Hz, 2 H), 4.03 (t, J = 7.2 Hz, 1 H), 3.63 (ABq, J = 12.6 Hz, $\Delta\nu$ = 63.7 Hz, 2 H), 3.08 (d, J = 12.2 Hz, 1 H), 2.62–2.46 (m, 2 H), 2.34–2.24 (m, 1 H), 2.09–1.69 (m, 7 H), 1.52–1.40 (m, 1 H), 1.38–1.34 (m, 1H), 1.36 (s, 3 H), 1.33 (s, 3 H), 1.31 (s, 3 H), 1.17–1.10 (m, 2 H), 1.08 (s, 3 H); ^{13}C NMR (62.5 MHz, C_6D_6) ppm 211.6, 148.4, 140.7, 128.6, 127.3, 127.0, 120.6, 99.8, 81.1, 77.3, 66.1, 65.9, 64.9, 55.6, 51.9, 45.3, 35.5, 33.6, 25.5, 25.3, 25.0, 24.1, 23.1, 23.0, 22.6, 21.4; FAB MS m/z (M^+ + 1) calcd 455.28, obsd 455.40; $[\alpha]^{21}_D$ −31.9° (c 0.68, $CHCl_3$). Anal. Calcd for $C_{28}H_{38}O_5$: C, 73.98; H, 8.43. Found: C, 73.79; H, 8.46.

(4a*S*,6a*S*,9*R*,12*E*,14a*R*,14b*R*)-14b-(Benzyloxy)-1,4a,5,6,-6a,8,9,10,11,14,14a,14b-dodecahydro-6a-hydroxy-3,3,15,15-tetramethyl-9,12-methano-7*H*-cyclodeca[*f*][1,3]benzodioxin-7-one (42). A benzene solution (2 mL) of **40** (24 mg, 0.055 mmol) and 18-crown-6 (54 mg, 0.20 mmol) was treated with potassium hexamethyldisilazide (0.60 mL of 0.50 M in toluene, 0.30 mmol) without provision for excluding O_2, stirred at rt for 1.5 h, and quenched with saturated NH_4Cl solution (1 mL). After dilution with water (5 mL), the product was extracted into ether (2 × 15 mL), dried, concentrated, and purified by flash chromatography (silica gel, gradient elution with 10:1 to 5:1 hexane–ethyl acetate) to give **42** (20 mg, 79%) as a colorless solid, mp 144–146 °C (from benzene-hexane); IR (film, cm^{-1}) 3480 (br), 1685, 1500, 1460, 1385, 1235, 1100, 1070; ^1H NMR (300 MHz, C_6D_6) δ 7.41 (d, J = 7.3 Hz, 2 H), 7.25–7.12 (m, 3 H), 5.24 (d, J = 11.6 Hz, 1 H), 4.78 (d, J = 11.9 Hz, 1 H), 4.72 (d, J = 12.6 Hz, 1 H), 4.65 (d, J = 11.9 Hz, 1 H), 4.13 (t, J = 2.9 Hz, 1 H), 3.85 (d, J = 12.6 Hz, 1 H), 2.97 (dd, J = 12.1, 1.1 Hz, 1 H), 2.51–2.38 (series of m, 12 H), 1.46 (s, 3 H), 1.42 (s, 3 H), 1.38–1.26 (m, 1 H), 1.32 (s, 3 H), 1.14–1.08 (m, 1 H), 1.04 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 215.2, 148.4, 140.4, 128.5, 127.5, 127.4, 120.4, 99.2, 81.6, 79.8, 69.2, 65.6, 63.7, 57.2, 52.3, 45.3, 35.6, 34.6, 25.9, 25.4, 24.9, 24.7, 24.6, 24.4, 22.6, 21.2; FAB MS m/z (M^+ + 1) calcd 455.28, obsd 455.40; $[\alpha]^{23}_D$ −104° (c 0.62, $CHCl_3$). Anal. Calcd for $C_{28}H_{38}O_5$: C, 73.98; H, 8.43. Found: C, 73.62; H, 8.53.

(4a*S*,9*R*,12*E*,14a*R*,14b*R*)-14b-(benzyloxy)-1,4a,5,8,9,10,11,-14,14a,14b-decahydro-3,3,15,15-tetramethyl-9,12-methano-7*H*-cyclodeca[*f*][1,3]benzodioxin-7-one (43). A CH_2Cl_2 solution (2 mL) of **42** (6 mg, 0.014 mmol) was cooled to 0 °C under nitrogen, treated with triethylamine (0.05 mL, 0.36 mmol) and methanesulfonyl chloride (10.0 μL, 0.13 mmol), warmed gradually to rt during 2 h, and quenched with water (5 mL). The product was extracted into CH_2Cl_2 (2 × 10 mL), dried, concentrated, and purified by flash chromatography on silica gel (gradient elution with 20:1 to 15:1 hexane–ethyl acetate) to give **43** (3 mg, 46%) as a colorless oil; IR (neat, cm^{-1}) 1650, 1380, 1245, 1195, 1100; ^1H NMR (300 MHz, C_6D_6) δ 7.28 (d, J = 7.2 Hz, 2 H), 7.13–7.01 (m, 3 H), 5.68 (t, J = 3.6 Hz, 1 H), 5.32 (dd, J = 11.0, 4.6 Hz, 1 H), 4.58 (d, J = 10.7 Hz, 1 H), 4.10–4.07 (m, 2H), 3.98 (d, J = 11.2 Hz, 1 H), 3.87 (d, J = 11.2 Hz, 1 H), 3.80 (dd, J = 12.3, 5.4 Hz, 1 H), 3.34 (dd, J = 24.1, 12.2 Hz, 1 H), 2.66–2.41 (m, 4 H), 2.36 (dd, J = 13.5, 2.3 Hz, 1 H), 2.10 (dd, J = 20.1, 3.5 Hz, 1 H), 2.02–1.85 (m, 2 H), 1.69–1.64 (m, 1 H), 1.43 (s, 3 H), 1.38 (s, 3 H), 1.31 (s, 3 H), 1.29–1.19 (m, 1 H), 0.98 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 205.6, 148.2, 141.9, 139.5, 128.4, 128.2, 127.6, 126.9, 123.0, 99.0, 70.3, 69.8, 67.5, 64.0, 48.3, 46.10, 46.07, 39.6, 29.9, 29.7, 29.0, 27.6, 26.3, 24.4, 20.3, 18.6; MS m/z (M^+) calcd 436.2613, obsd 436.2591; $[\alpha]^{22}_D$ −230° (c 0.56, $CHCl_3$). Anal. Calcd for $C_{28}H_{36}O_4$: C, 77.03; H, 8.31. Found: C, 76.71; H, 8.49.

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Supplementary Material Available: 300-MHz ^1H and 75-MHz ^{13}C NMR spectra of **8**, **10**, **27**, **28**, **29**, **32**, **33**, **35**, and **37** together with crystallographic experimental details, ORTEP diagram, tables of bond distances and angles, final fractional coordinates, and thermal parameters for **42**, as well as the final computed atomic coordinates for **41** (25 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.